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CLINICAL LIVER

Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications

Pierre Nahon,[1,2,3] Valérie Bourcier,[1] Richard Layese,[4] Etienne Audureau,[4] Carole Cagnot,[5] Patrick Marcellin,[6] Dominique Guyader,[7] Hélène Fontaine,[8] Dominique Larrey,[9] Victor De Lédinghen,[10] Denis Ouzan,[11] Fabien Zoulim,[12] Dominique Roulot,[13] Albert Tran,[14,15] Jean-Pierre Bronowicki,[16] Jean-Pierre Zarski,[17] Vincent Leroy,[17] Ghassan Riachi,[18] Paul Calès,[19] Jean-Marie Péron,[20] Laurent Alric,[21] Marc Bourlière,[22] Philippe Mathurin,[23] Sébastien Dharancy,[23] Jean-Frédéric Blanc,[24] Armand Abergel,[25] Lawrence Serfaty,[26] Ariane Mallat,[27] Jean-Didier Grangé,[28] Pierre Attali,[29] Yannick Bacq,[30] Claire Wartelle,[31] Thông Dao,[32] Yves Benhamou,[33] Christophe Pilette,[34] Christine Silvain,[35] Christos Christidis,[36] Dominique Capron,[37] Brigitte Bernard-Chabert,[38] David Zucman,[39] Vincent Di Martino,[40] Vincent Thibaut,[41] Dominique Salmon,[42] Marianne Ziol,[2,3,43,44] Angela Sutton,[44,45,46] Stanislas Pol,[8,47] and Françoise Roudot-Thoraval,[4] for the ANRS CO12 CirVir Group

[1]AP-HP, Hôpital Jean Verdier, Service d'Hépatologie, Bondy, France; [2]Université Paris 13, Sorbonne Paris Cité, "Equipe Labellisée Ligue Contre le Cancer," Saint-Denis, France; [3]Inserm, UMR-1162, "Génomique Fonctionnelle des Tumeur Solides," Paris, France; [4]AP-HP, Hôpital Henri Mondor, Département de Santé Publique, and Université Paris-Est, Ageing-Thorax-Vessels-Blood Département Hospitalo-Universitaire, Clinical Epidemiology and Aging Unit, Université Paris-Est Créteil, Créteil, France; [5]Unit for Basic and Clinical Research on Viral Hepatitis, Association Nationale pour la Recherche sur le SIDA et les hépatites virales (ANRS), France REcherche Nord and sud Sida-HIV Hépatites, Paris, France; [6]AP-HP, Hôpital Beaujon, Service d'Hépatologie, Clichy, France; [7]Centre Hospitalo-Universitaire Pontchaillou, Service d'Hépatologie, Rennes, France; [8]AP-HP, Hôpital Cochin, Département d'Hépatologie, [9]Hôpital Saint Eloi, Service d'Hépatologie, Montpellier, France; [10]Hôpital Haut-Lévêque, Service d'Hépatologie, Bordeaux, France; [11]Institut Arnaud Tzanck, Service d'Hépatologie, St Laurent du Var, France; [12]Hospices Civils de Lyon, Service d'Hépatologie et Université de Lyon, Lyon, France; [13]AP-HP, Hôpital Avicenne, Service d'Hépatologie, Bobigny, France; [14]Centre Hospitalo-Universitaire de Nice, Service d'Hépatologie, Nice, France; [15]Inserm U1065, C3M, Team 8, "Hepatic Complications in Obesity," Nice, France; [16]Inserm 954, Centre Hospitalo-Universitaire de Nancy, Université de Lorraine, Vandoeuvre-les-Nancy, France; [17]Hôpital Michallon, Service d'Hépatologie, Grenoble, France; [18]Hôpital Charles-Nicolle, Service d'Hépatologie, Rouen, France; [19]Centre Hospitalo-Universitaire d'Angers, Service d'Hépato-Gastroentérologie, Angers, France; [20]Hôpital Purpan, Service d'Hépatologie, Toulouse, France; [21]Centre Hospitalo-Universitaire Toulouse, Service de Médecine Interne-Pôle Digestif UMR 152, Toulouse, France; [22]Hôpital Saint Joseph, Service d'Hépatologie, Marseille, France; [23]Hôpital Claude Huriez, Service d'Hépatologie, Lille, France; [24]Hôpital St André, Service d'Hépatologie, Bordeaux, France; [25]Hôpital Hôtel Dieu, Service d'Hépatologie, Clermont-Ferrand, France; [26]AP-HP, Hôpital Saint-Antoine, Service d'Hépatologie, Paris, France; [27]AP-HP, Hôpital Henri Mondor, Service d'Hépatologie, Créteil, France; [28]AP-HP, Hôpital Tenon, Service d'Hépatologie, Paris, France; [29]AP-HP, Hôpital Paul Brousse, Service d'Hépatologie, Villejuif, France; [30]Hôpital Trousseau, Unité d'Hépatologie, Centre Hospitalier Régional Universitaire de Tours, France; [31]Hôpital d'Aix-en-Provence, Service d'Hépatologie, Aix-En-Provence, France; [32]Hôpital de la Côte de Nacre, Service d'Hépatologie, Caen, France; [33]AP-HP, Groupe Hospitalier de La Pitié-Salpêtrière, Service d'Hépatologie, Paris, France; [34]Centre Hospitalo-Universitaire Le Mans, Service d'Hépatologie, Le Mans, France; [35]Centre Hospitalo-Universitaire de Poitiers, Service d'Hépatologie, Poitiers, France; [36]Institut Mutualiste Montsouris, Service d'Hépatologie, Paris, France; [37]Hôpital Amiens Nord, Service d'Hépatologie, Amiens, France; [38]Hôpital Robert Debré, Service d'Hépatologie, Reims, France; [39]Hôpital Foch, Service de Médecine Interne, Suresnes, France; [40]Hôpital Jean Minjoz, Service d'Hépatologie, Besançon, France; [41]Centre Hospitalo-Universitaire Pontchaillou, Service de Virologie, Rennes, France; [42]AP-HP, Hôpital Cochin, Service de Maladies Infectieuses, Université Paris Descartes, Paris, France; [43]AP-HP, Hôpital Jean Verdier, Service d'Anatomopathologie, Bondy, France; [44]Centre de Ressources Biologiques (Liver Disease Biobank) Groupe Hospitalier Paris, Seine-Saint-Denis, France; [45]AP-HP, Hôpital Jean Verdier, Service de Biochimie, Bondy, France; [46]Inserm U1148, Université Paris 13, Bobigny, France; [47]Inserm UMS20 et U1223, Institut Pasteur, Université Paris Descartes, Paris, France

BACKGROUND & AIMS: We performed a prospective study to investigate the effects of a sustained viral response (SVR) on outcomes of patients with hepatitis C virus (HCV) infection and compensated cirrhosis. **METHODS:** We collected data from 1323 patients included in the prospective Agence Nationale pour la Recherche sur le SIDA et les hépatites virales (ANRS) viral cirrhosis (CirVir) cohort, recruited from 35 clinical centers in France from 2006 through 2012. All patients had HCV infection and biopsy-proven cirrhosis, were Child–Pugh class A, and had no prior liver complications. All patients received anti-HCV treatment before or after inclusion (with interferon then with direct antiviral agents) and underwent an ultrasound examination every 6 months, as well as endoscopic evaluations. SVR was considered as a time-dependent covariate; its effect on outcome was assessed by the Cox proportional hazard regression method. We used a propensity score to minimize confounding by indication of treatment and capacity to achieve SVR. **RESULTS:** After a median follow-up period of 58.2 months, 668 patients (50.5%) achieved SVR. SVR

was associated with a decreased incidence of hepatocellular carcinoma (hazard ratio [HR] compared with patients without an SVR, 0.29; 95% confidence interval [CI], 0.19–0.43; $P < .001$) and hepatic decompensation (HR, 0.26; 95% CI, 0.17–0.39; $P < .001$). Patients with SVRs also had a lower risk of cardiovascular events (HR, 0.42; 95% CI, 0.25–0.69; $P = .001$) and bacterial infections (HR, 0.44; 95% CI, 0.29–0.68; $P < .001$). Metabolic features were associated with a higher risk of hepatocellular carcinoma in patients with SVRs, but not in patients with viremia. SVR affected overall mortality (HR, 0.27 compared with patients without SVR; 95% CI, 0.18–0.42; $P < .001$) and death from liver-related and non–liver-related causes. Similar results were obtained in a propensity score-matched population. **CONCLUSIONS:** We confirmed a reduction in critical events, liver-related or not, in a prospective study of patients with HCV infection and compensated cirrhosis included in the CirVir cohort who achieved an SVR. We found an SVR to reduce overall mortality and risk of death from liver-related and non–liver-related causes. A longer follow-up evaluation is required to accurately describe and assess specific risk factors for complications in this population.

Keywords: ANRS CirVir; HCV Clearance; Direct Antivirals; Prognosis.

Hepatitis C virus (HCV)-infected cirrhotic patients have the lowest rates of sustained viral response (SVR) across all genotypes and treatment regimens[1] and are exposed to both hepatic[2] and extrahepatic life-threatening complications.[3] Moreover, cirrhotic patients often present with a high prevalence of comorbidities.[4] The clinical benefits of achieving SVR in this population have been estimated only in national registries,[5] retrospective cohorts,[6] or meta-analyses of observational studies,[7] which all suggested a decreased risk of liver-related complications and mortality[8] and possibly extrahepatic events. These data suggesting long-term benefits of HCV eradication, however, are considered as moderate-quality evidence because of the design and implementation of these aforementioned studies in heterogeneous populations without histologic staging of liver injury. The extent to which such assumptions are true remains to be confirmed prospectively, as does the question of whether viral eradication effects extend beyond liver-related complications and mortality.[9] However, prospective cohorts of HCV-treated cirrhotic patients are lacking. Longitudinal approaches require a long follow-up period to record sufficient numbers of events and to enable performing complex multivariable analyses taking into account all confounding factors, including competing risks of death.[10] In particular, those related to extrahepatic complications such as bacterial infection (BI), cardiovascular disease, or extrahepatic malignancies often are not reported accurately in the absence of prospective design[11] because they often rely on indirect outcome events such as International Classification of Disease codes or retrospective data collection, which can be subject to errors.[12]

Recent introduction of direct-acting antivirals (DAAs)[13] has lead to viral eradication in most patients, including patients with comorbidities and more severe cirrhosis owing to the safety profile of these treatments. Because the clinical benefits of second-generation DAAs will require several years of follow-up evaluation, we currently must rely on long-term results obtained in patients treated by interferon (IFN)-based regimens (with or without first-generation antiprotease) to elucidate the incidence, characteristics, and predictive factors of all complications (liver-related or not) expected in forthcoming years.

The French ANRS CO12 CirVir prospective cohort was intended to address these issues. Based on a rigorous approach including prospective multicentric inclusion of viral-infected compensated patients with biopsy-proven cirrhosis, the protocol-driven systematic data collection of clinical events ensures quality of analyses in a potentially competing risk framework.[14,15] Baseline characteristics of the ANRS CO12 CirVir cohort and a brief description of the first events occurring during follow-up evaluation have been reported.[15] In the present study, specific focus on outcomes occurring during a longer follow-up evaluation of this population according to SVR status (particularly after a DAA-based regimen) was performed. The aim of the present report was to evaluate prospectively the impact of SVR in a large population of cirrhotic individuals by accurately detailing clinical benefits of viral clearance over the entire spectrum of complications usually observed in these patients. Analyses particularly took into account the influence of comorbidities in patients treated by interferon-based regimens and also focused on the risk factors for complications occurring after SVR, including in the first patients treated by second-generation DAAs.

Materials and Methods

This study was sponsored and funded by the ANRS. Protocol approval was obtained from the Ethics Committee (Comité de Protection des Personnes, Aulnay-sous-Bois, France) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent to participate in the cohort. The full CirVir protocol is available on the ANRS website (http://anrs.fr).

Patient Selection

The present work is an ancillary study derived from the CirVir cohort[14] with specific goals and objectives redefined according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[16] Patients were recruited in 35 French clinical centers between 2006 and 2012. Selection criteria were as follows: (1) age older than 18 years; (2)

Abbreviations used in this paper: **AFP, α-fetoprotein; ANRS CO12 CirVir, Agence Nationale pour la Recherche sur le SIDA et les hépatites virales cohort 12 viral cirrhosis; BI, bacterial infection; CumI, cumulated incidence; DAA, direct antiviral agent; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IFN, interferon; IQR, interquartile range; MACE, major adverse cardiac event; MD, missing data; Peg-IFN, peg-interferon; PLC, primary liver cancer; RBV, ribavirin; SBP, spontaneous bacterial peritonitis; SVR, sustained virologic response; US, ultrasonography.**

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histologically proven cirrhosis, whatever the time of biopsy; (3) HCV antibody positive, whatever the level of viral replication; (4) absence of previous complications of cirrhosis (particularly ascites, gastrointestinal hemorrhage, or hepatocellular carcinoma [HCC]); (5) patients belonging to Child–Pugh class A; and (6) absence of severe uncontrolled extrahepatic disease resulting in an estimated life expectancy of less than 1 year. Preinclusion assessment included the usual clinical and biological parameters; patients with metabolic features were defined by a body mass index of 25 kg/m^2 or greater and/or diabetes and/or dyslipidemia at baseline. Missing biological data were assessed on frozen serum samples provided by the CRB (liver disease biobank Groupe Hospitalier Paris Seine-Saint-Denis BB-0033-00027). A Doppler ultrasonography (US) examination also was performed to check inclusion and noninclusion criteria. Patient information was recorded in a computerized database by a clinical research associate specifically dedicated to the ANRS CO12 CirVir cohort in each center. For all patients, past and ongoing alcohol and tobacco consumption were quantified and recorded at inclusion. Past medical history also was recorded.

Follow-Up Evaluation

Patients were seen by physicians every 6 months, and the usual clinical and biological data were recorded. Examination by Doppler US was performed every 6 months. For a given patient, it was recommended that 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. In cases of a focal liver lesion detected by US, a diagnostic procedure using contrast-enhanced imaging (computed tomography scan or magnetic resonance imaging), serum α-fetoprotein (AFP) assay, and/or a guided biopsy was performed according to the 2005 American Association for the Study of Liver Diseases guidelines,[17] updated in 2011.[18] HCC diagnosis thus was established either by histologic examination performed by an experienced pathologist or by using probabilistic noninvasive criteria (mainly dynamic imaging showing early arterial hypervascularization and portal washout) according to the different time period (before and after 2011). When HCC diagnosis was established, treatment was determined using a multidisciplinary approach according to the American Association for the Study of Liver Diseases guidelines for HCC.[17,18] All patients were followed up uniformly according to these international recommendations, irrespective of SVR status.

Regular endoscopic surveillance was performed. In case of esophageal varices, preventive therapy was recommended using either β-blockers or endoscopic ligation.[19]

All events occurring during follow-up evaluation, liver-related or not, were recorded based on information obtained from medical files of patients from each center. In particular, all episodes of liver decompensation encompassing ascites, hepatic encephalopathy, and gastrointestinal bleeding were described, as well as their severity, management according to international recommendations, and outcome.[19,20] All extrahepatic events occurring during the follow-up period also were recorded. There was a specific focus on BIs, with criteria for diagnosis of infections as described elsewhere.[21] Because of their high prevalence in this population, cardiovascular events and the occurrence of extrahepatic cancers were monitored carefully. We also defined a subgroup of patients affected by major adverse cardiac events (MACE),[22] which were restricted to stroke, ischemic heart disease, cardiovascular death, cardiac arrest, and heart failure. Likely cause(s) of death were established. Patients who underwent liver transplantation were censored at the date of transplantation for analysis. All treatments including antiviral therapy were recorded at inclusion, and any modification during follow-up evaluation was noted, in particular in case of severe adverse events. All recorded information during the follow-up evaluation was monitored secondarily by the same panel of 3 clinical research associates located at AP-HP, Hôpital Jean Verdier, Service d'Hépatologie, Bondy, Université Paris 13. All medical diagnoses of events occurring during follow-up evaluation were confirmed by 2 senior hepatologists (V.B. and P.N.). When a given event occurred during an interferon-based treatment, it clearly was recorded in the database.

Antiviral Treatment and Viral Replication

Because the inclusion period took place before 2012 and analyses of data were conducted in January 2016, most antiviral therapies administered during the follow-up evaluation were interferon-based. Patients with HCV genotype 1 or 4 infection received pegylate (peg)-interferon (Peg-IFN) plus a standard dose of ribavirin (RBV; 1000 mg/day if body weight was $<$75 kg or 1200 mg/day if body weight was $>$75 kg) for 48 weeks. Patients with HCV genotype 2 or 3 infection received Peg-IFN plus low-dose RBV (800 mg/day) for 16 or 24 weeks. After 2011, genotype 1 patients also could receive either 12 weeks of telaprevir (750 mg every 8 hours) in combination with Peg-IFN and RBV, then 36 weeks of Peg-IFN/RBV, or 4 weeks (lead-in phase) of Peg-IFN and RBV and then 44 weeks of Peg-IFN/RBV and boceprevir (800 mg every 8 hours) according to the European label. Since February 2014, sofosbuvir-containing regimens have become progressively available for cirrhotic patients in France and are prescribed and reimbursed for all HCV genotypes. The primary efficacy outcome was SVR, defined as an undetectable HCV-RNA level by qualitative polymerase chain reaction assay ($<$50 IU/mL) at the end of a 12-week untreated follow-up period.[23] An event arbitrarily was considered as occurring in a patient who achieved SVR if it was recorded at least 1 year after successful treatment completion.

Statistical Analyses

Descriptive results were presented as medians (interquartile range [IQR]) for continuous variables and as numbers (percentages) for categoric data. Baseline characteristics were compared between the 3 groups of patients classified according to SVR status using 1-way analysis of variance or the Kruskal–Wallis rank-sum test for continuous variables. HCC characteristics were compared between patients with SVR and without SVR using the Student t test or the Wilcoxon rank-sum test for continuous variables. Categoric variables were compared using the chi-squared test or the Fisher exact test if necessary.

The SVR effect on occurrence of HCC, liver failure, BI, vascular events, extrahepatic cancers, overall mortality, and liver and non–liver-related mortality was assessed by the Cox proportional hazards regression method. End of treatment was defined as time 0 for patients with SVR during follow-up evaluation because patients with undetectable HCV RNA at that time were considered to have SVR status. SVR was included as a time-dependent covariate in Cox regression because a non-SVR

patient could be re-treated and such re-treatment could result in SVR. Fixed SVR values were used for patients who never experienced SVR (SVR, 0) and patients with SVR at the time of their inclusion (SVR, 1). Non-SVR patients at inclusion who achieved SVR status during follow-up evaluation were switched from non-SVR to SVR status, considering the end of treatment that led to undetectable HCV-RNA level as the time point for setting SVR values from 0 to 1. No re-infection or relapse, as defined by a detectable HCV-RNA level in a patient who previously achieved SVR, was observed during the follow-up period.

Predictive analysis of baseline features associated with risk of complications and death were tested using univariate and multivariate Cox models. Assumptions allowing Cox regression use were verified. A sensitivity analysis based on a competing risk approach (Fine and Gray method) was performed to assess the effect of overall death as a competing event on the occurrence of the outcome of interest. Results from Cox and Fine–Gray approaches then were compared. To take into account confounding by indication of treatment and capacity to achieve SVR, we also used a propensity score, built using all variables that were different between the SVR and non-SVR groups (see Supplementary Tables 5 and 8–10). Risk of complications and death then were tested by multivariate Cox models on the subgroup of 630 patients matched on propensity score.[24,25]

Cumulative incidence and survival curves according to SVR status were built using the Kaplan–Meier method, completed by a clock reset approach.

Comparison of incidence and survival curves according to SVR status was assessed with univariate Cox regression analyses, with SVR as a time-dependent covariate.

All statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). A P value less than .05 was considered statistically significant.

Results

Inclusion Period and Baseline Characteristics of Patients

A total of 1822 cirrhotic patients were included (Table 1). Among them, 151 subsequently were excluded from analysis after revision of individual data owing to either noncompliance with inclusion criteria (n = 142) or consent withdrawal (n = 9). Consequently, final analyses were performed in 1671 patients, among whom 1323 had HCV-related compensated cirrhosis and constituted the study population (Supplementary Figure 1). For analysis, the reference date was December 31, 2015. At that date, the median duration of follow-up evaluation was 58.2 months (IQR, 36.6–79.0 mo).

Evolution of Viral Replication During Follow-Up Evaluation

Table 1 reports the characteristics of patients according to virologic status at baseline and during follow-up evaluation. Although 1235 (93.5%) patients were undergoing or previously had undergone antiviral therapy at inclusion, the rates of negative viral load at the time of inclusion were low (n = 389; 29.5%) and corresponded to SVR in 258 (20.0%) patients. During follow-up evaluation, an additional total of 1183 treatments were recorded in 793 patients, among whom 287 contained a first-generation antiprotease agent in genotype 1 patients (telaprevir or boceprevir) and 328 a DAA-containing regimen. Only 179 of these DAA-based treatments were assessable for SVR at end point. The duration from inclusion to treatment was 0.5 months (IQR, 0–19.4 mo). At the end point in December 2015, SVR assessment was available in 1291 (97.6%) patients. At that date, the number (rate) of HCV patients with a negative viral load was 787 (59.5%). Among the latter, this observation corresponded to a SVR at end point in 668 patients (51.7%), whereas the remaining 119 HCV-negative patients still were undergoing antiviral treatment at this time, mostly based on second-generation DAAs. Apart from patients with SVR at inclusion, baseline characteristics were similar between patients reaching SVR during follow-up evaluation and patients without SVR (Table 1). SVR differed according to genotype, as follows: genotype 1, 381 of 829 (46.0%); genotype 2, 46 of 69 (66.7%); genotype 3, 120 of 187 (64.2%); genotype 4, 49 of 113 (43.4%); genotypes 5 and 6, 12 of 20 (60.0%). Independent predictive factors for SVR were as follows: male sex (hazard ratio [HR], 1.28; 95% CI, 1.07–1.54; P = .007), absence of esophageal varices (HR, 1.27; 95% CI, 1.04–1.54; P = .016), and absence of diabetes (HR, 1.40; 95% CI, 1.11–1.76; P = .004). The median duration of follow-up evaluation after SVR was 31.2 months (IQR, 11.7–62.9 mo; minimum duration, 0.03 mo; maximum duration, 110.1 mo).

Patients With SVR Had a Lower Incidence of Liver-Related Complications

During follow-up evaluation, a first hepatic focal lesion was observed in 422 patients (31.9%) with a 5-year cumulated incidence (CumI) estimated as 34.0%. After a diagnostic procedure, more than half of these focal liver lesions remained indeterminate or were considered benign (n = 230; 54.5%). A definite diagnosis of primary liver cancer (PLC) was established in the remaining 192 patients: HCC (n = 186) and intrahepatic cholangiocarcinoma (n = 6). The PLC 5-year CumI was 14.4%.

The characteristics of HCC at diagnosis are shown in Supplementary Table 1. Overall, a large majority of patients with HCC were within Milan criteria, and curative treatment as first-line therapy was performed in most of them. SVR was associated with a decreased risk of HCC occurrence (Figure 1*A*).

In patients with SVR, 28 HCCs were diagnosed (Supplementary Table 1). At diagnosis, as compared with patients without SVR, rates of HCC within Milan criteria as well as implementation of treatment in a curative attempt were similar. Intervals between the last 2 imaging examinations before HCC diagnosis also were comparable. The median serum AFP level at the time of HCC diagnosis was lower in patients with SVR, in whom high levels, greater than 200 ng/mL, were never reported. Survival of HCC patients from HCC diagnosis was improved in SVR patients (3-year CumI, 66.3% vs 49.3%; P = .031). Causes of death in SVR patients (n = 4) all were secondary to HCC progression whereas patients without SVR still died of complications of liver failure or extrahepatic diseases (n = 24 of 68; 35.3%; missing data [MD], 4) (Supplementary Figure 2).

Table 1. Baseline Characteristics of Patients at Inclusion According to Virologic Status

Characteristics	All patients (n = 1323)	Patients with virologic status, n	SVR at inclusion (n = 258; 20.0%)	SVR during follow-up evaluation (n = 410; 31.8%)	Without SVR (n = 623; 48.3%)	*P* value[a]
Male sex	839 (63.4)	1291	172 (66.7)	272 (66.3)	375 (60.2)	.07
Age, *y*	55.4 (48.9–64.4)	1291	56.4 (48.8–62.9)	54.4 (48.2–62.3)	56.0 (49.6–66.9)	.001
Platelet count, $10^3/mm^3$	136.0 (96.0–182.0)	1269	179.0 (139.5–224.5)	133.5 (98.0–178.0)	124.0 (89.0–164.0)	<.001
AST, *IU/mL*	58.0 (35.0–92.0)	1288	28.0 (23.0–36.0)	66.0 (42.0–101.0)	71.0 (47.0–104.0)	<.001
ALT, *IU/mL*	63.0 (35.0–108.0)	1288	27.0 (21.0–39.0)	83.0 (46.0–129.0)	74.0 (49.0–115.0)	<.001
GGT, *IU/mL*	85.0 (47.0–160.5)	1288	39.0 (24.0–71.0)	87.0 (53.0–157.5)	111.5 (67.0–196.0)	<.001
Serum albumin, *g/L*	41.6 (38.0–44.8)	1280	44.0 (41.6–46.9)	41.5 (38.3–44.8)	40.3 (37.0–43.7)	<.001
Bilirubin, *μmol/L*	12.0 (8.0–16.0)	1288	9.0 (6.0–13.0)	11.0 (8.0–16.0)	13.0 (9.0–18.0)	<.001
Prothrombin time, %	89.0 (79.0–98.0)	1250	91.0 (81.0–100.0)	89.0 (79.0–97.0)	87.0 (78.0–98.0)	.002
Creatinine, *μmol/L*	71.0 (61.9–81.0)	1281	73.0 (63.0–81.0)	70.7 (61.9–80.2)	70.7 (61.0–81.0)	.05
GFR (MDRD formula)[b]	96.7 (81.9–113.2)	1281	94.0 (81.1–108.9)	100.0 (83.6–115.9)	95.7 (81.4–112.1)	.024
Esophageal varices	332 (31.0)	1043	53 (25.6)	83 (25.3)	184 (36.2)	.001
HCV genotype		1218				
1	849 (67.9)		98 (46.5)	283 (71.3)	448 (73.4)	
2	69 (5.5)		29 (13.7)	17 (4.3)	23 (3.7)	
3	195 (15.6)		60 (28.4)	60 (15.1)	67 (11.0)	<.001
4	115 (9.2)		18 (8.5)	31 (7.8)	64 (10.5)	
5	18 (1.5)		4 (1.9)	5 (1.3)	7 (1.2)	
6	4 (0.3)		2 (1.0)	1 (0.2)	1 (0.2)	
Anti-HBc antibodies		1281				.77
Negative	846 (64.4)		169 (66.3)	264 (64.5)	393 (63.7)	
Positive	467 (35.6)		86 (33.7)	145 (35.5)	224 (36.3)	
HIV co-infection	56 (4.6)	1124	5 (2.3)	11 (5.0)	36 (5.3)	.19
Past excessive alcohol consumption	406 (32.1)	1234	83 (34.4)	119 (30.3)	189 (31.5)	.55
Ongoing alcohol consumption, *g/day*		1196				
0	918 (74.9)		179 (74.3)	287 (75.7)	429 (74.5)	
<10	193 (15.8)		38 (15.7)	64 (16.9)	89 (15.4)	
10–50	91 (7.4)		18 (7.5)	22 (5.8)	47 (8.2)	.63[c]
50–100	18 (1.5)		6 (2.5)	3 (0.8)	9 (1.6)	
>100	5 (0.4)		0	3 (0.8)	2 (0.3)	
Tobacco consumption		1202				
Never	491 (39.9)		88 (37.0)	158 (41.6)	238 (40.8)	
Past	276 (22.5)		61 (25.6)	79 (20.8)	131 (22.4)	.66
Ongoing	462 (37.6)		89 (37.4)	143 (37.6)	215 (36.8)	
Substance or drug abuse		1266				
Never	889 (68.5)		172 (69.4)	269 (66.3)	431 (70.4)	
Past	400 (30.8)		74 (19.8)	135 (33.2)	176 (28.8)	.60
Ongoing	9 (0.7)		2 (0.8)	2 (0.5)	5 (0.8)	
BMI, kg/m^2	25.8 (23.0–28.8)	1138	26.0 (23.2–29.1)	25.6 (23.1–28.7)	25.9 (22.8–28.9)	.73
BMI class		1138				
<25	487 (41.9)		84 (37.2)	160 (44.6)	231 (41.8)	
25–30	457 (39.3)		98 (43.3)	134 (37.3)	216 (39.1)	.51
≥30	218 (18.8)		44 (19.5)	65 (18.1)	106 (19.1)	
Diabetes	253 (19.1)	1291	39 (15.1)	64 (15.6)	143 (23.0)	.003
Dyslipidemia	69 (5.2)	1291	10 (3.9)	24 (5.9)	34 (5.5)	.52
Arterial hypertension	373 (28.2)	1291	62 (24.0)	104 (25.4)	197 (31.6)	.024
Past history of CV events	115 (8.7)	1291	17 (6.6)	29 (7.1)	67 (10.8)	.048
Past history of malignancy	55 (4.2)	1291	6 (2.3)	19 (4.6)	28 (4.5)	.27

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CV, cardiovascular; GFR, glomerular filtration rate; GGT, γ-glutamyltransferase; HBc, hepatitis B core; HIV, human immunodeficiency virus; MDRD, modification of diet in renal disease.

[a]Comparison between the 3 groups.

[b]$GFR = 186.3 \times (\text{creatinine } (\mu mol/L)/88.4)^{-1.154} \times age^{-0.203} \times k$; where k = 1 for men and k = 0.742 for women.

[c]*P* value obtained by the following regroupment of modalities of variable alcohol consumption (1, 0 or <10; 2, 10–50; and 3, >50).

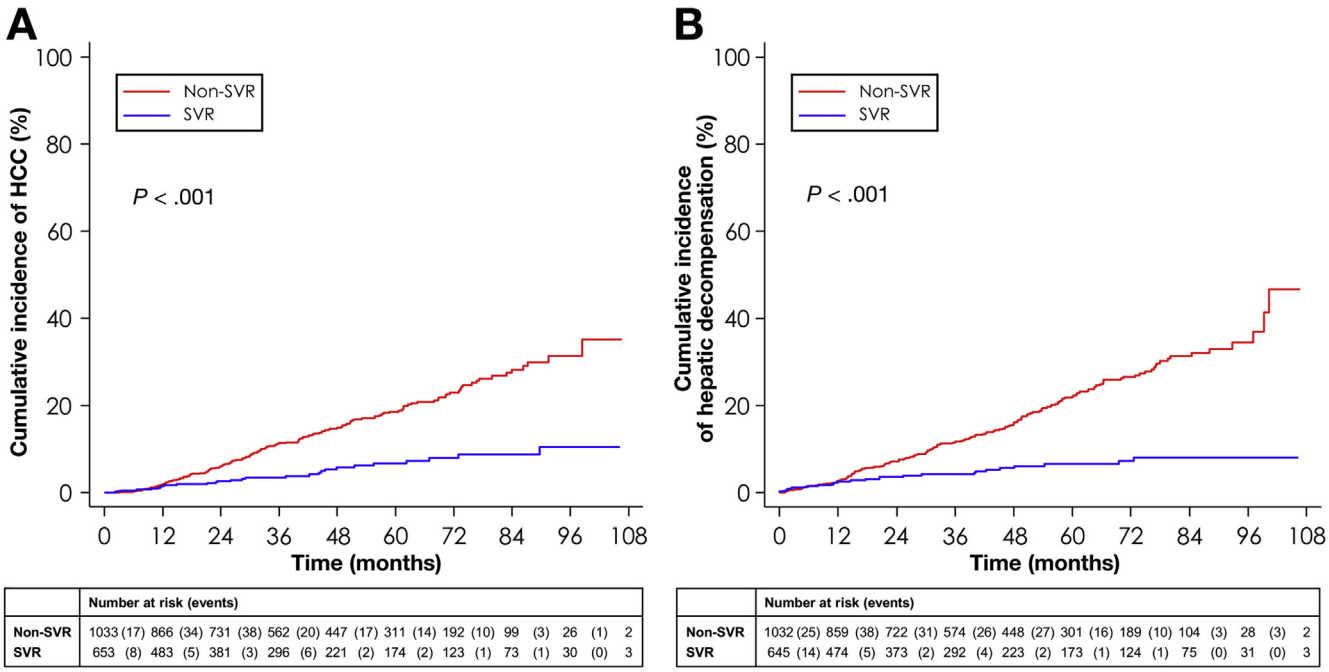


Figure 1. Incidence of liver complications according to SVR. (*A*) HCC (5-year CumI, 18.5% vs 6.7%; HR, 0.28; 95% CI, 0.19–0.43; $P < .001$). (*B*) Hepatic decompensation (5-year CumI, 22.0% vs 6.5%; HR, 0.26; 95% CI, 0.17–0.39; $P < .001$).

Overall, 215 patients (16.3%) presented with at least 1 episode of liver decompensation, defined by the occurrence of either ascites (n = 171), hepatic encephalopathy (n = 61), or gastrointestinal bleeding (related to portal hypertension in 33 of 67), with a corresponding 5-year CumI of 16.7%. SVR was associated with a decreased risk of liver decompensation (Figure 1*B*). SVR patients who experienced subsequent liver decompensation had an overall more pronounced impairment of liver function at baseline (Supplementary Table 2). Of note, only 20 of the 395 decompensations (5.1%) were observed during the course of an interferon-based regimen.

Decreased Incidence of Extrahepatic Disease in SVR Patients

A total of 1550 extrahepatic events in 697 patients were recorded. In the present analyses, we focused on occurrences of BI, extrahepatic cancers, and vascular events.

A total of 140 vascular events occurred in 103 patients (heart failure, 33; ischemic heart disease, 30; cardiac arrhythmia, 19; stroke, 23; valvular cardiopathy, 11; peripheral arterial obstructive disease, 10; cardiac arrest, 6; aortic aneurysm, 1; and others, 7). Patients who achieved SVR had a lower risk of cardiovascular events and MACE (Figure 2*A* and Supplementary Figure 3). Genotype did not influence the risk of cardiovascular event (Supplementary Tables 3–5).

A total of 204 patients experienced a first symptomatic episode of BI, corresponding to a 5-year CumI of 16.2%. The main localizations were urinary tract infection (27.0%), pulmonary infections (24.5%), spontaneous bacterial peritonitis (SBP) (10.8%), and skin infections (12.2%). Other sites of infection were reported in 52 (25.5%) other cases. Because of the vicious circle between liver decompensation and infections, longitudinal analyses were restricted to BIs occurring before any episode of decompensation, which finally concerned 148 patients. Patients who experienced SVR had a subsequent decreased risk of BI (Figure 2*B*). Patients who received a protease inhibitor (PI) regimen had a higher risk of BI occurrence, a finding that did not, however, impact prognosis in the long term in the present study (Supplementary Tables 6 and 7).

Ninety-six extrahepatic cancers were reported in 83 patients (15 lymphomas and hemopathies, 15 gynecologic, 12 colon and rectum, 12 lungs, 12 oral, 8 other digestive, 3 prostate, 7 skin, and 12 other) with a corresponding 5-year incidence of 6.5%. SVR did not influence the occurrence of extrahepatic malignancies (Figure 2*C*). In particular, risk of occurrence of lymphomas and hemopathies was similar for SVR and non-SVR patients (5-year CumI, 1.4% vs 1.3%; $P = .87$).

SVR Is a Protective Factor Against Hepatic and Extrahepatic Complications

Table 2 summarizes results of multivariate analyses. SVR exerted an independent protective impact on most of these events, liver-related or not. Results from a sensitivity analysis based on a competing risk approach are shown in Supplementary Figure 4 and found the competing effect of death to be negligible, with similar findings obtained from Cox and Fine–Gray approaches. To further examine the stability of our findings, a supporting analysis was conducted based on propensity-matching (Supplementary Tables 8–10, Supplementary Figure 5). In addition, these results were confirmed by multivariate Cox regressions performed in a propensity-matched population (Table 3).

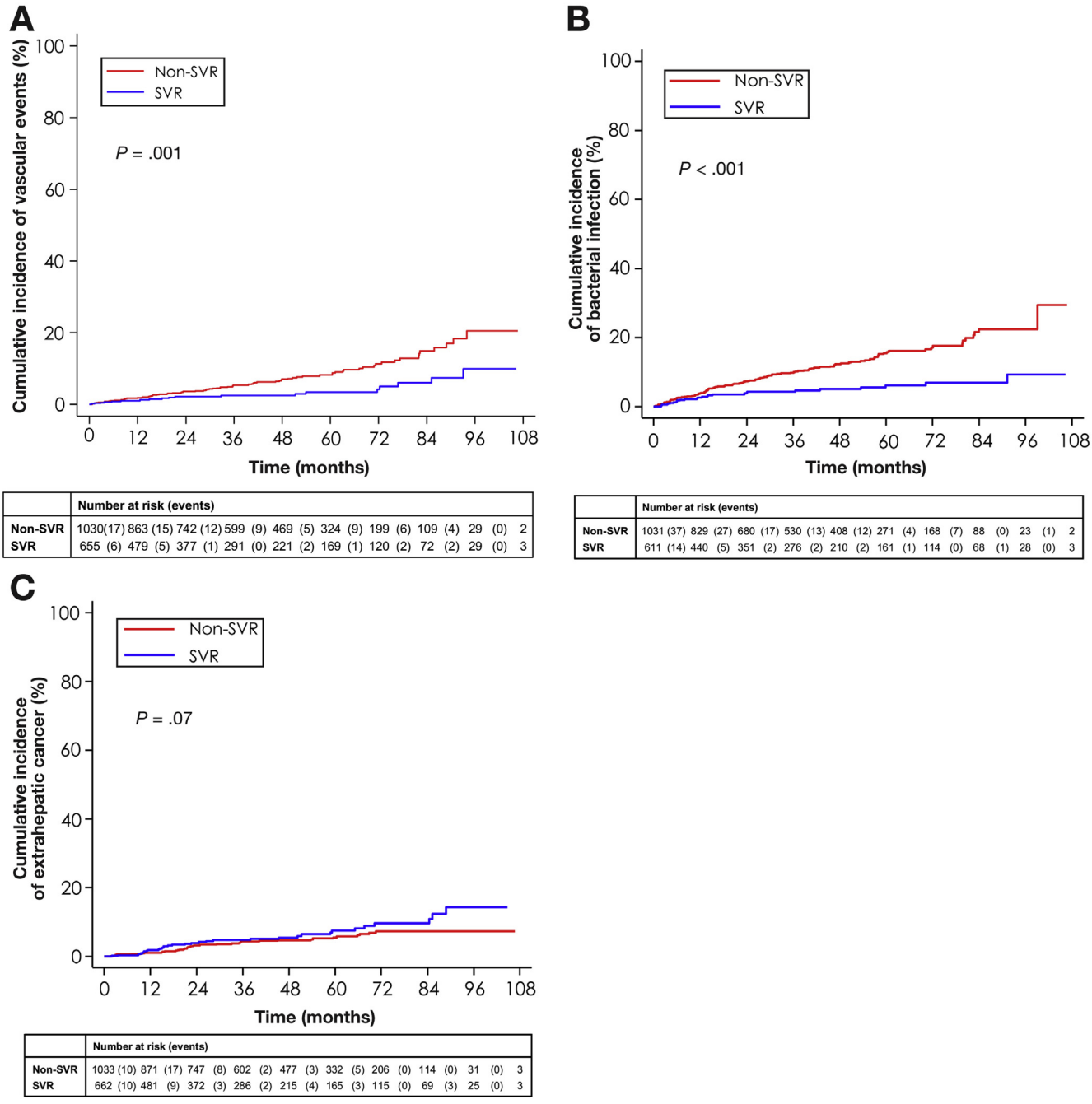


Figure 2. Incidence of extrahepatic complications according to SVR. (*A*) Vascular events (5-year CumI, 8.1% vs 3.4%; HR, 0.42; 95% CI, 0.25–0.69; $P = .001$). (*B*) Bacterial infection (5-year CumI, 15.5% vs 6.2%; HR, 0.44; 95% CI, 0.29–0.68; $P < .001$). (*C*) Extrahepatic cancers (5-year CumI, 5.4% vs 7.5%; HR, 1.52; 95% CI, 0.96–2.39; $P = .07$).

Among SVR patients, HCC occurrence was associated with the following variables: lower prothrombin time (PT) less than 80% ($P = .001$), lower platelet count less than $100.10^3/mm^3$ ($P = .050$), higher γ-glutamyltransferase level greater than the upper limit of normal ($P = .006$), higher aspartate aminotransferase level greater than the upper limit of normal ($P = .010$), and features of metabolic syndrome (defined by body mass index ≥ 25 kg/m^2 and/or diabetes and/or dyslipidemia) ($P = .042$). SVR patients who had combined features of metabolic syndrome had an intermediate risk of HCC occurrence because only 1 case of HCC was observed in SVR patients without metabolic syndrome (Figure 3).

HCV-Infected Cirrhotic Patients Achieving SVR Had Decreased Overall and Specific Mortality

In the entire cohort, 175 patients (13.2%) died during the follow-up evaluation, which corresponded to a 5-year survival rate of 88.6%. During follow-up evaluation, 39 patients were transplanted, 27 for end-stage liver disease and 12 for HCC. Ninety-one patients (58.0%) died of

Table 2. Features Associated With Occurrence of Complications in Patients With Compensated HCV-Related Cirrhosis According to Cox Proportional Hazards Model: Results of Multivariate Analyses

	HCC		Bacterial Infection		Decompensation		Overall death		Extrahepatic cancer		MACE		Cardiovascular events	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age[a]	1.91 (1.31–2.79)	.001	1.83 (1.14–2.92)	.012	1.42 (1.05–1.93)	.024	1.04 (1.02–1.05)	<.001	1.04 (1.01–1.06)	.001				
Platelet count, $10^3/mm^3$		<.001				<.001		<.001						
<100	2.26 (1.53–3.33)	<.001			3.05 (2.04–4.57)	<.001	2.25 (1.51–3.36)	<.001						
100–150	1.73 (1.17–2.55)	.006			1.26 (0.81–1.95)	.31	1.08 (0.70–1.66)	.73						
>150	Ref				Ref		Ref							
GGT levels		.003				<.001		.005						
≤N	Ref				Ref		Ref							
N–2 N	2.15 (1.27–3.64)	.004			1.76 (1.01–3.05)	.045	2.43 (1.42–4.14)	.001						
>2 N	2.38 (1.45–3.89)	.001			2.56 (1.55–4.22)	<.001	2.04 (1.23–3.39)	.006						
Albumin, *g/L*											2.27 (1.19–4.32)	.013		
≤35			2.02 (1.30-3.16)	.002	2.05 (1.43–2.94)	<.001	2.36 (1.60–3.49)	<.001			Ref		1.89 (1.12–3.22)	.018
>35			Ref		Ref		Ref						Ref	
GFR (MDRD formula)			0.99 (0.98–1.00)	.007										
Past excessive alcohol consumption	1.57 (1.14–2.15)	.005					1.53 (1.07–2.18)	.020						
Tobacco consumption												.037		
Never											Ref			
Past											1.73 (0.93–3.23)	.09		
Ongoing											2.15 (1.18–3.91)	.012		
Past history of CV events							1.76 (1.12–2.77)	.014			3.29 (1.82–5.95)	<.001	3.14 (1.93–5.10)	<.001
Arterial hypertension											2.27 (1.36–3.78)	.002	2.06 (1.35–3.14)	.001
Diabetes														
β-blocker intake[b]													1.57 (1.02–2.43)	.042
Esophageal varices					1.47 (1.07–2.00)	.016								
SVR[b]	0.41 (0.27–0.63)	<.001	0.49 (0.32–0.75)	.001	0.45 (0.29–0.69)	<.001	0.42 (0.27–0.67)	<.001	1.63 (1.04–2.57)	.035	0.53 (0.29–0.97)	.039	0.49 (0.29–0.82)	.007

CV, cardiovascular; GGT, γ-glutamyltransferase; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease.

[a]Age was studied as a categoric variable: age > 50 years for Cox models analyzing HCC and bacterial infection occurrence, age > 60 years for Cox model analyzing decompensation occurrence. For the Cox models analyzing extrahepatic cancer, vascular events, MACE, and overall death occurrence, age was studied as a quantitative variable.

[b]Included as a time-dependent variable.

Table 3. Features Associated With Occurrence of Complications in Patients With Compensated HCV-Related Cirrhosis According to Cox Proportional Hazards Model on the Propensity Score-Matched Population: Results of Multivariate Analyses

	HCC		Bacterial infection		Cardiovascular events		Decompensation		Overall death		Extrahepatic cancer		MACE	
Variables	HR (95% CI)	*P*	HR 95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age[a]			2.20 (1.12–4.33)	.022										
Platelet count, $10^3/mm^3$		.048						<.001						
<100	1.77 (1.06–2.98)	.030					4.20 (2.51–7.04)	<.001						
100–150	1.77 (1.07–2.90)	.025					1.69 (0.96–2.97)	.07						
>150	Ref						Ref							
GGT levels		.042												
≤N	Ref													
N–2 N	2.16 (1.05–4.44)	.036												
>2 N	2.39 (1.21–4.71)	.012												
Albumin, *g/L*														
≤35							2.12 (1.27–3.54)	.004	2.45 (1.37–4.38)	.002				
>35							Ref		Ref					
Total bilirubin, μmol/L														
≤17													Ref	
>17													2.03 (1.05–3.93)	.036
Tobacco consumption						.010								.025
Never					Ref								Ref	
Past					1.11 (0.50–2.49)	.80							1.75 (0.74–4.12)	.20
Ongoing					2.49 (1.33–4.69)	.005							2.92 (1.35–6.34)	.007
Substance or drug abuse								<.001						
Never							Ref							
Past							0.70 (0.44–1.12)	.14						
Ongoing							3.53 (1.99–6.29)	<.001						
Past history of CV events					2.64 (1.24–5.59)	.011							3.54 (1.57–7.99)	.002

Table 3. Continued

Variables	HCC		Bacterial infection		Cardiovascular events		Decompensation		Overall death		Extrahepatic cancer		MACE	
	HR (95% CI)	*P*	HR 95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Arterial hypertension					3.37 (1.87–6.09)	<.001							2.88 (1.49–5.56)	.002
Diabetes											2.12 (1.03–4.35)	.042		
Esophageal varices							1.67 (1.09–2.55)	.018						
Past history of malignancy									2.26 (1.04–4.90)	.039				
SVR[b]	0.53 (0.31–0.90)	.019	0.44 (0.21–0.93)	.032	0.42 (0.18–0.99)	.049	0.50 (0.29–0.85)	.010	0.46 (0.26–0.82)	.009				

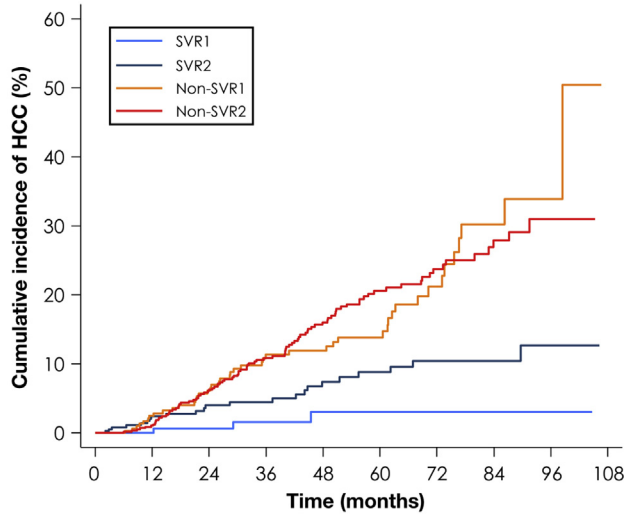
NOTE. There were 630 patients.
CV, cardiovascular; GGT, γ-glutamyltransferase.
[a]Age was studied as a categoric variable: age >50 years for Cox models analyzing HCC and bacterial infection occurrence, age >60 years for Cox model analyzing decompensation occurrence. For the Cox models analyzing extrahepatic cancer, vascular events, MACE, and overall death occurrence, age was studied as a quantitative variable.
[b]Included as a time-dependent variable.

liver-related complications, and 66 extrahepatic events (42.0%) were responsible for the remaining deaths (MD, 18). PLC progression was the first liver-related cause of death (n = 47; 30.0%), followed by complications of end-stage liver disease (n = 44; 28.0%). Major extrahepatic causes of death were BI (except SBP, n = 21), progression of extrahepatic cancer (n = 17), and cardiovascular diseases (n = 9) (others, n = 19). Only 26 deaths (3.9%) were recorded in SVR patients. SVR was a protective factor for all-cause mortality (Figure 4*A*), a finding that was translated into survival without liver-related (Figure 4*B*) or extrahepatic deaths (Figure 4*C*). Causes of death in SVR patients were as follows: extrahepatic cancer (n = 7), PLC progression (n = 6), portal hypertension (n = 2), liver failure (n = 2), and cardiovascular disease (n = 1) (other extrahepatic causes, n = 2; MD, n = 2). Table 2 shows independent features associated with overall death in the entire population, in which SVR was a protective factor selected by the multivariate model. This result also was confirmed in adjusting propensity score (Table 3). Among the 18 SVR patients who died during follow-up evaluation, independent features associated with a higher risk of death in this subgroup were as follows: lower platelet count less than $100.10^3/mm^3$ (HR, 2.46; 95% CI, 1.08–5.64; $P = .033$), presence of diabetes (HR, 3.00; 95% CI, 1.31–6.85; $P = .009$), a past history of cardiovascular events (HR, 4.64; 95% CI, 1.51–14.21; $P = .007$), and a past history of malignancy (HR, 6.55; 95% CI, 2.16–19.83; $P = .001$).

Analysis of heterogeneity of characteristics and outcomes by center size (≤10 patients vs >10 then ≤15 vs >15 patients enrolled) did not show any significant difference in main characteristics and outcomes across centers (Supplementary Tables 11–14). Overall, there was no difference in outcome in SVR patients, whether obtained after an interferon-based regimen or DAA, although the follow-up period in the latter group was too short to allow any definite conclusion (Supplementary Tables 15 and 16). Except for BI, interferon-based therapy did not influence the risk of extrahepatic disease (Supplementary Table 17).

Discussion

This prospective study based on follow-up evaluation of 1323 treated patients with biopsy-proven, HCV-related cirrhosis sought to compare the outcome of patients with and without SVR. Although the inclusion of patients in whom histologic assessment of fibrosis was mandatory might have introduced selection biases, this rigorous approach strengthens the confidence in the drawn conclusions given the risk of incorrectly staging fibrosis using noninvasive tests. Not surprisingly, patients with SVR differed from those with active infection in many characteristics, which are the main predictive factors of response to interferon therapy. Indeed, most patients included in these analyses performed in January 2015 had access to an interferon-based regimen between 2006 and 2014 because DAAs only became available in February 2014 in France in the setting of an early access program for cirrhotic patients. As a consequence, if 315 patients were undergoing a



	Number at risk (events)																	
SVR1	208	(0)	152	(1)	118	(1)	89	(1)	59	(0)	40	(0)	25	(0)	15	(0)	8	(0)	2
SVR2	378	(8)	289	(4)	230	(1)	186	(5)	147	(2)	121	(2)	91	(0)	56	(1)	22	(0)	1
Non-SVR1	316	(7)	264	(9)	214	(11)	172	(1)	142	(3)	100	(7)	53	(5)	22	(1)	5	(1)	0
Non-SVR2	624	(6)	524	(25)	447	(21)	342	(18)	272	(13)	187	(6)	126	(5)	71	(2)	20	(0)	2

Figure 3. Risk factors for HCC in SVR patients. Patients with metabolic features were defined by a body mass index of 25 kg/m^2 or greater and/or diabetes and/or dyslipidemia. The CirVir population was stratified according to SVR and metabolic features into 4 groups: SVR1, SVR patients without metabolic features; SVR2, SVR patients with metabolic features; non-SVR1, non-SVR patients without metabolic features; and non-SVR2, non-SVR patients with metabolic features. SVR1 patients had a lower risk of HCC compared with SVR2 patients (5-year CumI, 3.0% vs 8.8%; $P = .042$), whereas HCC risk was similar in non-SVR1 and non-SVR2 patients (5-year CumI, 13.9% vs 20.6%; $P = .91$).

DAA-based treatment at the time of analyses, only 179 of these regimens were assessable for SVR at end point. In a description of the CirVir cohort,[15] baseline viral load was associated with an increased incidence of all complications. The present report, with the advantage of a longer follow-up period and by studying virologic clearance at end point as a time-dependent covariate after an interferon- or DAA-based regimen, now clearly shows that achieving SVR in HCV-infected cirrhotic patients leads to an improved prognosis. Overall, the present data were able to highlight specifically the independent influence of SVR on the incidence of liver complications, including HCC and mortality, and, interestingly, a positive impact on the occurrence of extrahepatic manifestations. These findings were supported further by multivariate Cox regressions performed in a propensity-matched population (Table 3), suggesting a lack of confounding by indication of treatment and capacity to achieve SVR. This point also was supported by the analysis of patients who achieved SVR after DAA, who seemed to have a similar outcome although older and with more impaired liver function (Supplementary Table 15). However, the achievement of SVR in DAA-treated patients is too recent to draw any definite conclusion on this point, and will require a longer follow-up evaluation of the CirVir cohort to be addressed adequately. Our study also highlighted specific risk factors for complications occurring after HCV eradication, particularly the influence of metabolic features on HCC development in case of viral clearance.

The hepatic benefit of HCV clearance was suggested by the initial description of the CirVir cohort[14] because baseline viral load was associated with critical events occurring during the first 3 years of follow-up evaluation. The present data, by considering SVR as a time-dependent covariate over a longer follow-up period, provide a more accurate vision and stronger arguments on the expected clinical benefits on liver-related complications and death in case of HCV eradication. By rigorously analyzing the incidences of these complications in a competing risk framework, analysis of the CirVir cohort reports the precise rates of these events, particularly in patients with SVR, and confirms their dramatic decrease expected in forthcoming years, as predicted by modeling approaches.[26] These incidences are indeed strikingly low in nonviremic patients, usually less than 1% per year, but nevertheless continue to exist and to justify periodic screening policies, particularly HCC (Figure 1*A*).[27] Not surprisingly, these low rates of life-threatening events are translated into survival benefits, whether considering liver-related or extrahepatic mortality (Figure 4), thus delineating virologic cured HCV-related cirrhosis as a new clinical entity with specific risk factors for complications.

Except for lower levels of serum AFP that could be associated with HCV clearance, HCC characteristics did not differ according to SVR status (Supplementary Table 1). It is interesting to note that the few cases of HCC that developed in SVR patients occurred mainly in those with metabolic features (Figure 3). This could be explained by the known impact of diabetes and obesity in HCC development,[28] as well as by progression of fibrosis despite viral eradication in patients presenting with comorbidities. Metabolic features, however, did not exert the same impact on HCC development in patients with active HCV replication, although the lack of systematic record regarding changes of all parameters over time in the CirVir cohort constitutes a limitation in interpretation of these data. Such observation might reflect that HCV-related hepatocarcinogenesis may be less related to the biological consequences of insulin resistance than a direct oncogenic role of the virus. The influence of alcohol consumption in the CirVir cohort is minimal because most patients with a previous high alcohol intake stopped drinking or drank only a limited amount of alcohol during follow-up evaluation (although an unreliable declaration cannot be excluded). This was not the case for metabolic features, which were present in nearly 60% of SVR patients (Figure 3). The extent to which the occurrence of HCC in this population was associated with a specific oncogenic process, or progression/nonregression of fibrosis despite viral eradication, warrants future studies because it could pave the way for the development of specific pharmacologic targets in this population.

One of the most striking results of our study was the decrease in non–liver-related mortality in patients with SVR. This must be analyzed carefully according to causes of

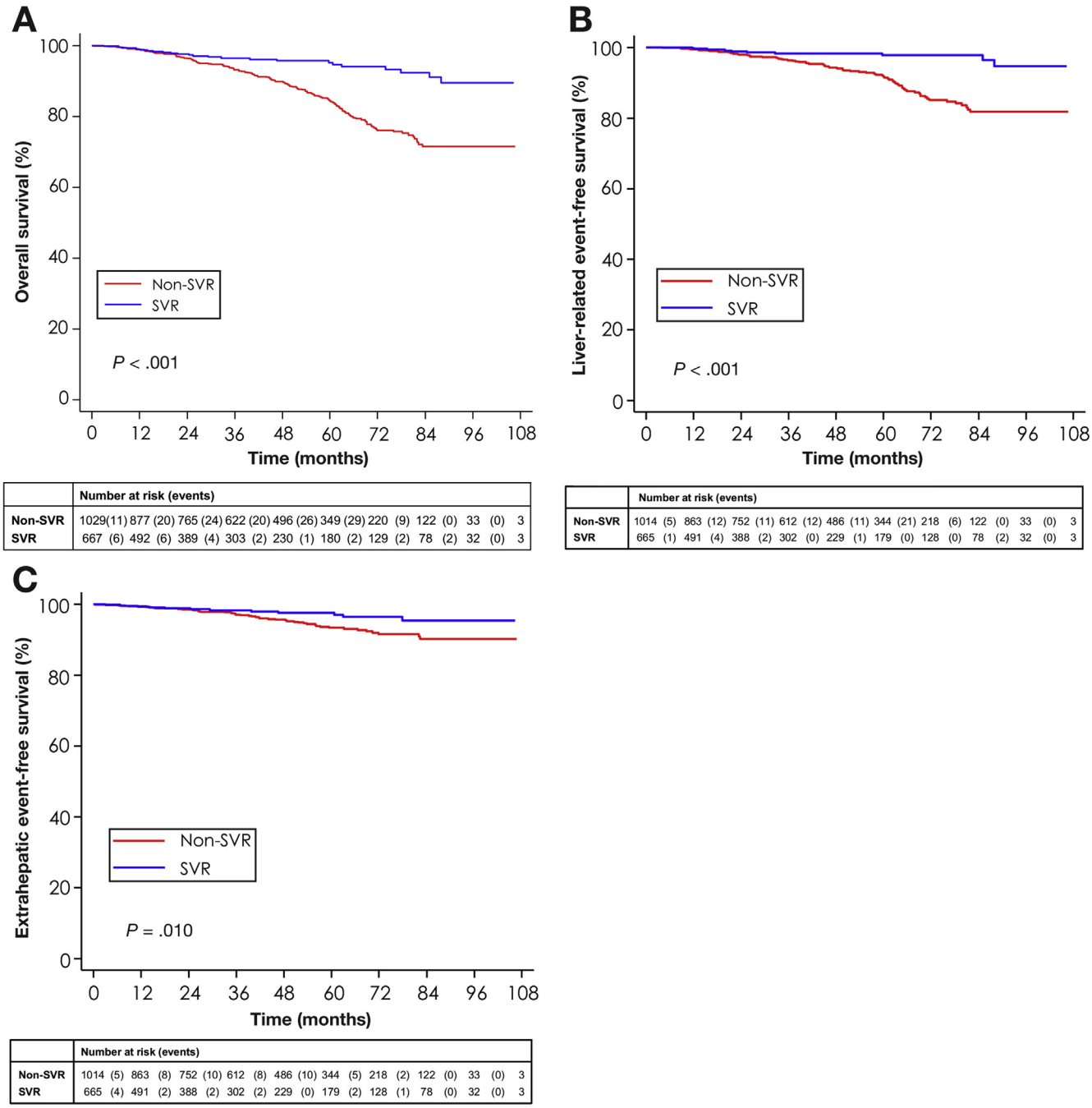


Figure 4. Survival according to SVR. (*A*) Overall mortality (5-year survival, 95.2% vs 84.5%; HR, 0.27; 95% CI, 0.18–0.42; $P < .001$). (*B*) Liver-related mortality (5-year specific survival, 97.8% vs 91.8%; HR, 0.19; 95% CI, 0.10–0.36; $P < .001$). (*C*) Extrahepatic mortality (5-year specific survival, 97.6% vs 93.4%; HR, 0.44; 95% CI, 0.24–0.82; $P = .010$).

death, mainly owing to BI, cardiovascular disease, and extrahepatic cancers, although the latter does not seem to be impacted by SVR. On the contrary, patients who achieved SVR had higher rates of extrahepatic malignancies (Table 2), an observation that might be related to the increased survival of this population (Figure 4). Until now, the possibility that the beneficial effects of SVR also result in reduced extrahepatic complications has been evoked only in retrospective studies focusing on an indirect end point, namely, all-cause mortality.[6] Therefore, deciphering the consequences of HCV eradication upon the occurrence of major causes of extrahepatic death would better justify the use of costly antiviral therapy, such as expensive second-generation DAAs.[29] This assumption is supported by the long-term observation of the CirVir cohort, because SVR was found to be an independent common predictor associated with a 2- to 5-fold reduction in all clinical complications (except for extrahepatic malignancies) (Figure 2*C*).

It is customary to consider BI as an extrahepatic complication, with the exception of SBP, classified in the

present study as liver-related. Despite this conventional view, several studies, including data from the CirVir cohort,[14] have shown that BIs in cirrhotic patients have prognostic significance; indeed, mortality is higher in patients who experienced a previous infection.[30] As a consequence, decreasing BI occurrence in compensated cirrhosis would constitute a major step toward improvement of cirrhosis management: it is tempting to speculate that the clinical benefit of HCV clearance over the long term might be explained not only by slower liver function impairment (Figure 1*B* and 2*B*), but also by disruption of a vicious circle triggered by end-organ-dysfunction–related BI.[31]

The link between SVR and vascular events might be indirect (Figure 2*A*), and possibly a consequence of overrepresentation of metabolic syndrome in patients without SVR, as well as contraindications to interferon-based treatment in patients with cardiac failure or severe coronary disease. In this regard, our findings should be interpreted with full consideration of the observational nature of the present study, in which reverse causation processes could not be ruled out completely for the associations hypothesized between SVR status and the outcomes. Nevertheless, experimental and clinical data have highlighted the complex interplay between HCV and glucose or lipid metabolism, with possible extrahepatic consequences.[32] However, although a higher incidence of vascular events has been reported in HCV-infected compared with uninfected patients,[33] it still is not clear whether HCV infection per se and/or its interference with metabolic/inflammatory dysfunctions triggers vascular injury. Convincing evidence suggests that HCV may directly promote cardiovascular disease. In particular, a correlation between the severity of liver necroinflammation caused by HCV infection and cardiovascular morbidity has been shown, possibly modulated by viral clearance.[34] Direct viral mechanisms, in addition to the negative impact of extensive fibrosis itself,[35] appear to promote atherosclerosis, as suggested by higher serum HCV-RNA levels in patients with vascular conditions,[36] or even by the presence of a positive HCV-RNA strand in carotid plaques of HCV-infected patients.[37] The positive impact of SVR on cardiovascular events is underlined further by the lower incidence of MACE observed in these patients (Table 2 and Supplementary Figure 3). Taken together, these considerations lend a new perspective to HCV infection, which could be considered a systemic disease in the course of which physicians carefully must assess vascular risk, particularly in case of cirrhosis. The extent to which such a potential decrease in vascular events and mortality in case of SVR will modify access to expensive new DAAs now must be evaluated by cost-effectiveness analyses.[38]

In summary, an overall decrease in critical events, whether liver-related or owing to extrahepatic causes, was observed in patients with HCV compensated cirrhosis achieving virologic clearance. If confirmed by the longer follow-up evaluation of increasing numbers of DAA-treated patients, this population will define a new clinical entity with a completely different outcome and increased survival. Identifying patients who will develop life-threatening complications despite viral eradication[39] that could be targeted selectively and in whom refinement of screening policies might be discussed constitutes a new challenge.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.09.009.

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Reprint requests
Address requests for reprints to: Pierre Nahon, MD, PhD, Service d'Hépato-Gastroentérologie, Hôpital Jean Verdier, 93140 Bondy, France. e-mail: pierre.nahon@jvr.aphp.fr; fax: (33) 1-48-02-62-02.

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Conflicts of interest

These authors disclose the following: Pierre Nahon has received honoraria from AbbVie, Bayer, Bristol-Myers Squibb, and Gilead, and consults for AbbVie and Bristol-Myers Squibb; Jean-Pierre Zarski consults and is on the speakers bureau for Gilead, Bristol-Myers Squibb, Janssen, Siemens, and MSD, and consults for AbbVie; Stanislas Pol consults for and has received grants from Bristol-Myers Squibb, Gilead, Roche, and MSD, and consults for Gilead, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, AbbVie, Roche, and MSD; Laurent Alric consults and has received grants from Bristol-Myers Squibb, MSD, and Gilead, and has received grants from Roche and Janssen; Marc Bourliere consults and advises for AbbVie, MSD, Janssen, Bristol-Myers Squibb, Roche, and Gilead; Vincent Di Martino consults and advises for Gilead and MSD, and advises for Janssen and Bristol-Myers Squibb; and Yannick Bacq consults for Roche, Bristol-Myers Squibb, and Gilead. The remaining authors disclose no conflicts.

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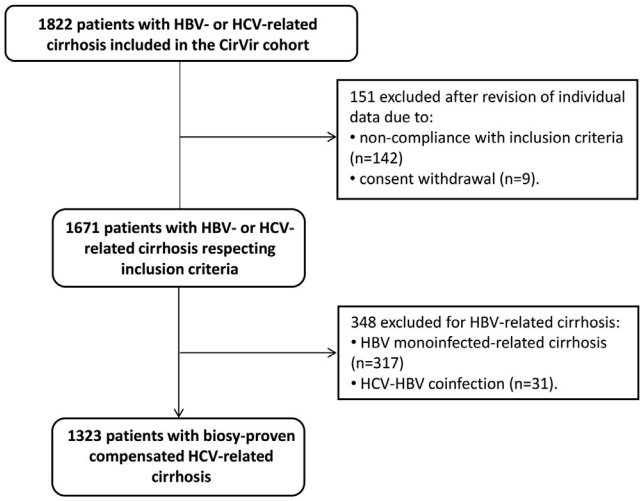
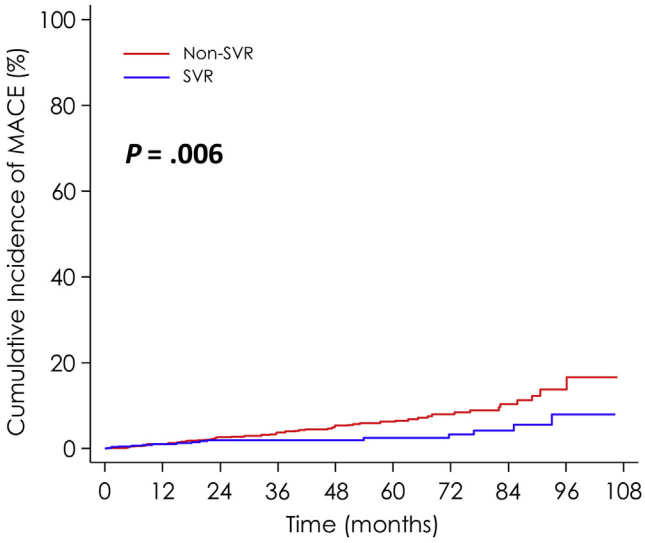
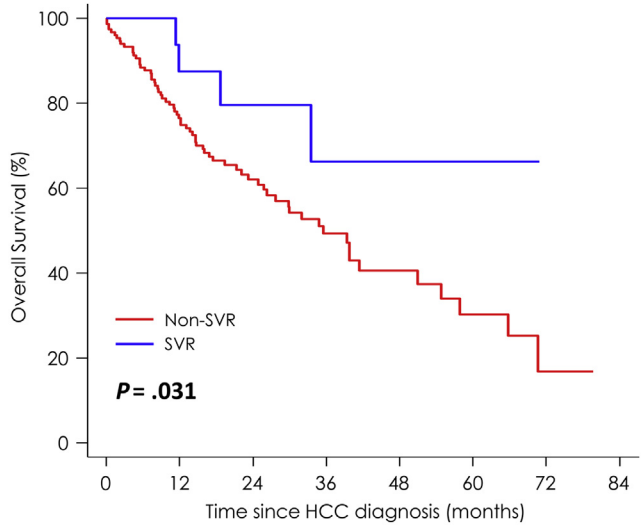


Supplementary Figure 1. Consort diagram. HBV, hepatitis B virus.



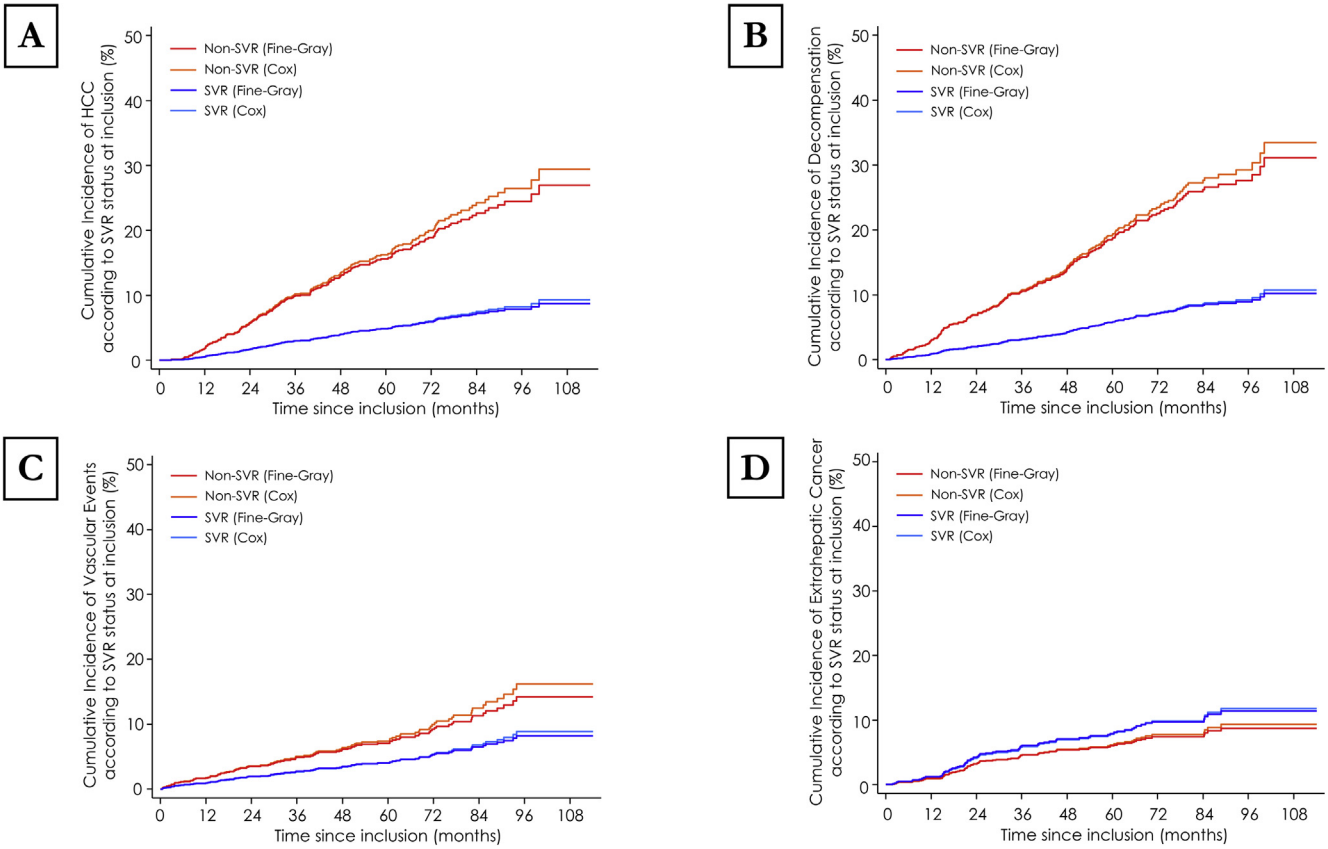
	Number at risk (events)																	
Non-SVR	1014	(9)	857	(13)	737	(8)	597	(8)	468	(4)	328	(5)	204	(4)	115	(3)	31	(1)	2
SVR	657	(6)	479	(4)	377	(0)	292	(0)	222	(1)	171	(1)	121	(1)	75	(2)	31	(0)	3

Supplementary Figure 3. Impact of SVR on MACE.

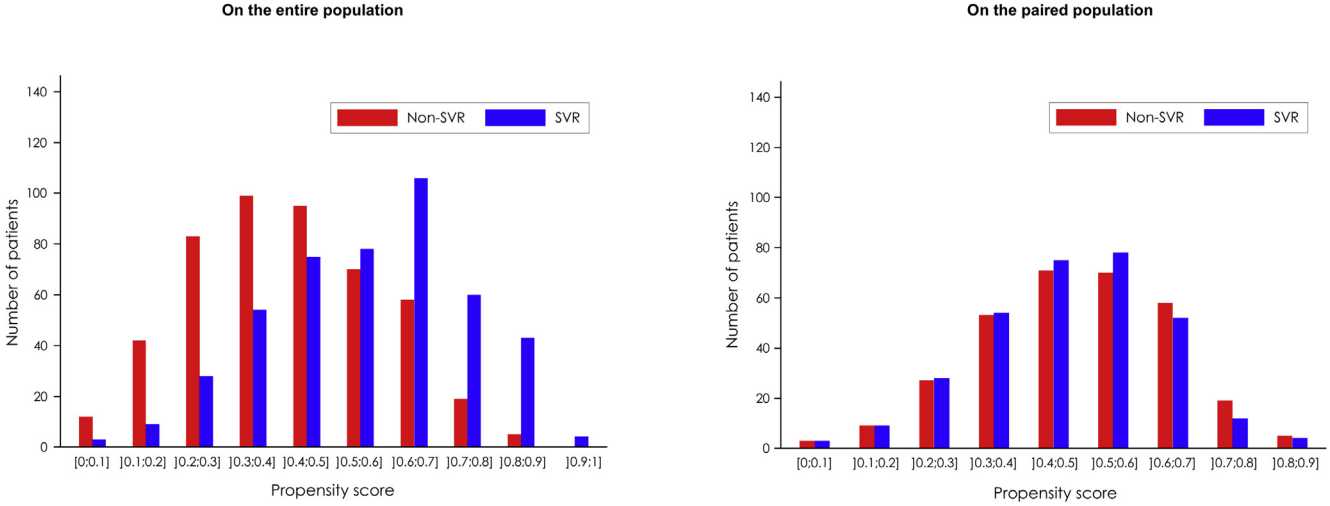


	Number at risk (events)														
Non-SVR	153	(33)	97	(16)	52	(9)	29	(4)	16	(3)	7	(2)	2	(0)	0
SVR	28	(2)	14	(1)	9	(1)	5	(0)	2	(0)	2	(0)	0	(0)	0

Supplementary Figure 2. Outcome of HCC patients according to SVR status.



Supplementary Figure 4. Competing risk analyses for occurrence of events during follow-up evaluation. (*A*) Hepatocellular carcinoma. (*B*) Hepatic decompensation. (*C*) Vascular events. (*D*) Extrahepatic malignancies.



Supplementary Figure 5. Distribution of propensity score on the entire population (*left*) and on the paired population (*right*).