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

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Abbreviations: BI: bacterial infection; DAA: direct antiviral agent; HCC: hepatocellular carcinoma; MACE: major adverse cardiac event; PLC: primary liver cancer; SBP: spontaneous bacterial peritonitis; SVR: sustained virological response.

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ABSTRACT

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 ANRS 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 direct antiviral agents) and underwent 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 an SVR. SVR was associated with a decreased incidence of hepatocellular carcinoma (HCC; hazard ratio [HR] compared to patients without an SVR=0.29; 95% 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 higher risk of HCC in patients with SVRs, but not in patients with viremia. SVR affected overall mortality (HR=0.27 compared to 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 is required to accurately describe and assess specific risk factors for complications in this population.

KEY WORDS: 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 co-morbidities.[4] The clinical benefits of achieving a sustained virological response (SVR) in this population have been estimated only in national registries,[5] retrospective cohorts[6] or meta-analyses of observational studies[7] which all suggest a decreased risk of liver-related complications and mortality[8] and possibly extrahepatic events. These data suggesting long-term benefits of HCV eradication are however considered as moderate-quality evidence, because of the design and implementation of these aforementioned studies in heterogeneous populations without histological staging of liver injury. The extent to which such assumptions are true remains to be prospectively confirmed, 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 in order 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 are often not accurately reported in the absence of prospective design[11], as they often rely upon indirect outcome events such as International Classification of Disease (ICD) codes or retrospective data collection which can be subject to errors.[12]

Recent introduction of direct-acting antivirals (DAAs)[13] leads to viral eradication in most patients, including those with co-morbidities and more severe cirrhosis due to the safety profile of these treatments. Because the clinical benefits of second-generation DAAs will require several years of follow-

up, we must currently rely on long-term results obtained in patients treated by interferon-based regimens (with or without first-generation anti-protease) 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 have been reported.[15] In the present study, specific focus on outcomes occurring during a longer follow-up of this population according to SVR status (particularly after DAA-based regimen) was undertaken.The aim of the present report was to prospectively evaluate 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 regimen and also focused on the risk factors for complications occurring after SVR, including in the first patients treated by second generation DAAs.

METHODS

This study was sponsored and funded by the ANRS. Protocol obtained approval 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 gave 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 STROBE statement.[16] Patients were recruited in 35 French clinical centers between 2006 and 2012. Selection criteria were: a) age older than 18 years; b) histologically proven cirrhosis, whatever the time of biopsy; c) HCV antibodies positive, whatever the level of viral replication; d) 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 estimated life expectancy of less than 1 year. Preinclusion assessment included the usual clinical and biological parameters; patients with metabolic features (MF) were defined by BMI≥25 kg/m^2 and/or diabetes and/or dyslipidaemia 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 was also undertaken to check inclusion and non inclusion criteria. Patient information was recorded in a computerized database by a clinical research associates specifically dedicated to the ANRS CO12 CirVir cohort in each center. For all patients, past and ongoing alcohol and tobacco consumptions were quantified and recorded at inclusion. Past medical history were also recorded.

Follow-up

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 centre by an experienced operator. A report was completed by each operator, mentioning the presence or not of focal liver lesions. In cases of focal liver lesion detected by US, 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[17] updated in 2011.[18] HCC diagnosis was thus established either by histological examination performed by an experienced pathologist or by using probabilistic non-invasive criteria (mainly dynamic imaging showing early arterial hypervascularisation and portal washout) according to the different periods of time (before and after 2011). When HCC diagnosis was established, treatment was determined using a multidisciplinary approach according to AASLD guidelines for HCC.[17, 18] All patients were followed-up uniformly according to these international recommendations irrespectively from SVR status. Regular endoscopic surveillance was performed. In case of oesophageal varices, preventive therapy was recommended using either beta-blockers or endoscopic ligation.[19]

All events occurring during follow-up, liver-related or not, were recorded based on information obtained from medical files of patients from each centre. In particular, all episodes of liver decompensation encompassing ascites, hepatic encephalopathy and gastro-intestinal bleeding were described, as well as their severity, management according to international recommendations and outcome.[19, 20] All extra-

hepatic events occurring during follow-up were also recorded. Specific focus on bacterial infections (BI) was undertaken, with criteria for diagnosis of infections as described elsewhere.[21] Because of their high prevalence in this population, cardiovascular events and the occurrence of extra-hepatic cancers were carefully monitored. 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 was notified, in particular in case of severe adverse events. All recorded information during follow-up was secondarily monitored by the same panel of 3 clinical research associates located at institution 1 (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, it was clearly precised in the database.

Antiviral treatment and viral replication

Since the inclusion period took place before 2012 and analyses of data were conducted in January 2016, most antiviral therapies conducted during follow-up were interferon-based. Patients with HCV genotype 1 or 4 infection received peg-interferon (Peg-IFN) plus a standard dose of ribavirin (RBV, 1,000 mg/day if body weight was<75 kg or 1,200 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 could also receive either 12 weeks of telaprevir (TVR, 750 mg every 8h) 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 (BOC, 800 mg every 8h) 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 sustained virological response (SVR), defined as undetectable HCV RNA by qualitative polymerase chain reaction (PCR) assay (<50 IU/mL) at the end of a 12-week untreated follow-up period.[23] 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.

Statistical analyses

Descriptive results were presented as median [interquartile range (IQR)] for continuous variables and as numbers (percentages) for categorical data. Baseline characteristics were compared between the three groups of patients classified according to SVR status using one-way ANOVA or 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 Wilcoxon rank sum test for continuous variables. Categorical variables were compared using the χ^2 test or exact Fisher 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, since 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, since a non-SVR patient could be retreated and such retreatment could result in a 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 were switched from non-SVR to SVR status, considering the end of treatment that led to undetectable HCV RNA as the time point for setting SVR values from 0 to 1. No re-infection or relapse, as defined by detectable HCV RNA in a patient who previously achieved SVR, was observed during the follow-up.

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 were then compared. In order to take into account confounding by indication of treatment and capacity to achieve SVR, we also used a propensity score, built using all variables different between SVR and Non-SVR groups (see Supplementary Material). Risk of complications and death were then tested by multivariate Cox models, on the subgroup of 630 patients matched on the 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 < 0.05 was considered statistically significant.

RESULTS

Inclusion period and baseline characteristics of patients (Table 1)

A total of 1,822 cirrhotic patients were included. Among them, 151 were subsequently excluded from analysis after revision of individual data due to either non-compliance with inclusion criteria (n=142) or consent withdrawal (n=9). Consequently, final analyses were performed in 1,671 patients, among whom 1,323 had HCV-related compensated cirrhosis and constituted the study population (See consort diagram, Supplementary Figure 1). For analysis, the reference date was December 31, 2015. At that date, median duration of follow-up was 58.2 months [36.6; 79.0].

Evolution of viral replication during follow-up

Table 1 reports the characteristics of patients according to virological status at baseline and during follow-up. Although 1,235 (93.5%) patients were undergoing or had previously undergone antiviral therapy at inclusion, 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, an additional total of 1,183 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. Duration from inclusion to treatment was 0.5 months [0 – 19.4]. At end-point in December 2015, SVR assessment was available in 1,291 (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%), while the remaining 119 HCV-negative patients were still undergoing antiviral treatment at this time, mostly based on second-generation DAA. Apart for patients with SVR at inclusion, baseline characteristics were similar between patients

reaching SVR during follow-up and patients without SVR (Table 1). SVR differed according to genotype: 1: 381/829 (46.0%), 2: 46/69 (66.7%), 3: 120/187 (64.2%), 4: 49/113 (43.4%), 5 and 6: 12/20 (60.0%). Independent predictive factors for SVR were: male gender (HR=1.28, [1.07; 1.54], P= .007), absence of esophageal varices (HR=1.27 [1.04; 1.54], P= .016) and absence of diabetes (HR=1.40 [1.11; 1.76], P= .004). The median duration follow-up after SVR was 31.2 months (IQR : [11.7 – 62.9]; minimum duration : 0.03 months; maximum duration : 110.1 months).

Patients with SVR had lower incidence of liver-related complications

During follow-up, a first hepatic focal lesion was observed in 422 patients (31.9%) with a 5-year cumulated incidence (CumI) estimated as 34.0%. Following 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 intra-hepatic cholangiocarcinoma (n=6). PLC 5-yr CumI was 14.4%.

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

In patients with SVR, 28 HCC were diagnosed (Supplementary Table 1). At diagnosis, as compared to 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 two imaging examinations before HCC diagnosis were also comparable. The median serum AFP level at time of HCC diagnosis was lower in patients with SVR, in whom high levels, above 200 ng/mL, were never reported. Survival of HCC patients from HCC diagnosis was improved in SVR patients (CumI 3-yr=66.3% vs 49.3% P= .031). Causes of death in SVR patients (n=4) were all secondary to HCC progression while patients without SVR still died of complications of liver failure or extrahepatic diseases [n=24/68, 35.3%, (MD=4)] (Supplementary Figure 2).

Overall, 215 patients (16.3%) presented at least one 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 out of 67), with a corresponding 5-yr CumI of 16.7%. SVR was associated with a decreased risk of liver decompensation (Figure 1B). 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 out 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 1,550 extrahepatic events in 697 patients were recorded. In the present analyses, we focused on occurrences of bacterial infection (BI), extrahepatic cancers and vascular events.

One hundred and forty 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; others, 7). Patients who achieved SVR had a lower risk of cardiovascular events and MACE (Figure 2A and Supplementary Figure 3). Genotype did not influence the risk of cardiovascular event (Supplementary Tables 3-5).

Two-hundred and four patients experienced a first symptomatic episode of BI, corresponding to a CumI 5-year of 16.2%. The main localizations were: urinary tract infection (UTI) (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 BI occurring before any episode of decompensation which finally concerned 148 patients. Patients who experienced SVR had a subsequent decreased risk of BI (Figure 2B). Patients who received a PI regimen had a higher risk of BI occurrence, a finding that did not however impact prognosis on the long term in the present study (Supplementary Tables 6 and 7).

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

SVR is a protective factor against hepatic and extrahepatic complications

Table 2 summarises results of multivariate analyses. SVR exerted an independent protective impact on most 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. In order to further examine the stability of our findings, a supporting analysis was conducted based on propensity-matching (Supplementary Tables 8-10). In addition, these results were confirmed by multivariate Cox regressions performed in a propensity-matched population (Table 3). Among SVR patients, HCC occurrence was associated with the following variables: lower PT<80% (P= .001), lower platelet count<$100.10^3/mm^3$ (P= .050), higher GGT level>ULN (P= .006), higher AST level>ULN (P= .010) and features of metabolic syndrome [defined by BMI≥25 kg/m^2 and/or diabetes and/or dyslipidemia] (P= .042). SVR patients who combined features of metabolic syndrome had an intermediate risk of HCC occurrence as only one 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 follow-up, which corresponded to 5-year survival of 88.6%. During follow-up, 39 patients were transplanted, 27 for end-stage liver disease and 12 for HCC. Ninety-one patients (58.0%) died of liver-related complications, while 66 extrahepatic events (42.0%) were responsible for the remaining deaths [MD=18]. PLC progression was the first liver-related causes of death (n=47, 30.0%), followed by complications of liver failure/portal hypertension (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 4A), a finding that was translated into survival without liver-related (Figure 4B) or extrahepatic deaths (Figure 4C). Causes of death in SVR patients were: 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 and MD, n=2]. Table 2 displays independent features associated with overall death in the entire population, in which SVR was a protective factor selected by the multivariate model. This result was also confirmed in adjusting on propensity score (Table 3). Among the 18 SVR patients who died during follow-up, independent features associated with higher risk of death in this subgroup were: lower platelet count<$100.10^3/mm^3$ (HR=2.46, [1.08; 5.64], P= .033), presence of diabetes (HR=3.00, [1.31; 6.85], P= .009), a past history of

cardiovascular events (HR=4.64, [1.51; 14.21], P= .007) and a past history of malignancy (HR=6.55, [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 reveal 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 interferon-based regimen or DAA, although the follow-up in the latter group is too short to allow any definite conclusion (Supplementary Tables 15-16). 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 of 1,323 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 histological assessment of fibrosis was mandatory might have introduced selection biases, this rigorous approach strengthens the confidence in the drawn conclusions given the risk of fibrosis misstaging using non-invasive 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 interferon-based regimen between 2006 and 2014 as DAA only became available in February 2014 in France in the setting of early-access program for cirrhotic patients. As a consequence, if 315 patients were undergoing a DAA-based treatment at the time of analyses, only 179 of these regimens were assessable for SVR at end-point. In the first 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 and by studying virological clearance at endpoint as a time-dependent covariate after 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 are able to specifically highlight 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 furthermore supported 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 is also supported by the analysis of patients who achieved SVR after DAA, who seem to have a similar outcome although older and with a 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, which will require a longer follow-up of the CirVir cohort to be adequately addressed. Our study also highlights 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] as baseline viral load was associated with critical events occurring during the 3 first years of follow-up. The present data, by considering SVR as a time-dependent covariate over a longer follow-up, 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 modelling approaches.[26] These incidences are indeed strikingly low in non viraemic patients, usually below 1% per year, but nevertheless continue to exist and to justify periodic screening policies, particularly HCC (Figure 1A).[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 “virological 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 co-morbidities. 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 insulinoresistance than a direct oncogenic role of the virus. The influence of alcohol consumption in the CirVir cohort is minimal, as most patients with a previous high alcohol intake stopped drinking or drank only a limited amount of alcohol during follow-up (although unreliable declaration cannot be excluded). This is not the case for metabolic features, present in nearly 60% of SVR patients (Figure 3). The extent to which the occurrence of HCC in this population is associated with a specific oncogenic process, or progression/non-regression of fibrosis despite viral eradication, warrants future studies, as it could pave the way for development of specific pharmacological 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 carefully analysed according to causes of death, mainly due to BI, cardiovascular disease and extrahepatic cancers although the latter event 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 endpoint, 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 DAA.[29] This assumption is supported by the long-term observation of the CirVir cohort, as 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 2C).

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 BI in cirrhotic patients has prognostic significance; indeed, mortality is higher in those who experienced previous infection.[30] As a consequence, decreasing BI occurrence in compensated cirrhosis would constitute a major step towards 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 1B and 2B), 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 2A), 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, where 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 to uninfected patients,[33] it is still 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 necro-inflammation caused by HCV infection and cardio-vascular 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 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 further underlined 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 must carefully 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 DAA must now be evaluated by cost-effectiveness analyses.[38]

In summary, an overall decrease in critical events, whether liver-related or due to extrahepatic causes, is observed in patients with HCV compensated cirrhosis achieving virological clearance. If confirmed by the longer follow-up 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 selectively targeted and in whom refinement of screening policies might be discussed constitutes a new challenge.

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FIGURE LEGENDS

Figure 1- Incidence of liver complications according to SVR. A. HCC (Cumulated incidence (CumI) 5-year: 18.5% vs 6.7%, HR=0.28 [0.19; 0.43], P< .001). B. Hepatic decompensation (CumI 5-year: 22.0% vs. 6.5%, HR=0.26 [0.17; 0.39], P< .001).

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

Figure 3. Risk factors for HCC in SVR patients. Patients with metabolic features (MF) were defined by BMI≥25 kg/m^2 and/or diabetes and/or dyslipidaemia. The CirVir population was stratified according to SVR and MF into four groups: SVR1 (SVR patients without MF), SVR2 (SVR patients and MF), Non-SVR1 (non-SVR patients without MF) and Non-SVR2 (non SVR patients and MS). SVR1 patients had a lower risk of HCC compared with SVR2 patients (CumI 5-year: 3.0% vs 8.8%, P= .042), while HCC risk was similar in Non-SVR1 and Non-SVR2 patients (CumI 5-year: 13.9% vs. 20.6%, P= .91).

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

Characteristics	All patients (n = 1323)	Number of patients with virological status	SVR at inclusion [n = 258 (20.0%)]	SVR during follow-up [n = 410 (31.8%)]	Without SVR [n = 623 (48.3%)]	P-value[a]
Male gender	839 (63.4)	1291	172 (66.7)	272 (66.3)	375 (60.2)	.07
Age (years)	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
Creatinin (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
Oesophageal 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

BMI: body mass index; SVR: sustained virological response; GFR: glomerular filtration rate; CV: cardiovascular

[a] Comparison between the three groups

[b] GFR = $186.3 \times (\text{creatinin } (\mu\text{mol/L}) / 88.4)^{-1.154} \times \text{age}^{-0.203} \times k$; 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”, 3: “> 50”]

Table 1. Baseline characteristics of patients at inclusion according to virological status.

Characteristics	All patients (n = 1323)	Number of patients with virological status	SVR at inclusion [n = 258 (20.0%)]	SVR during follow-up [n = 410 (31.8%)]	Without SVR [n = 623 (48.3%)]	P-value[a]
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
Dyslipidaemia	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

BMI: body mass index; SVR: sustained virological response; GFR: glomerular filtration rate; CV: cardiovascular

[a] Comparison between the three groups

[b] GFR = $186.3 \times (\text{creatinin } (\mu\text{mol/L}) / 88.4)^{-1.154} \times \text{age}^{-0.203} \times k$; 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”, 3: “> 50”]

Table 1. Baseline characteristics of patients at inclusion according to virological status (continued).

	HCC		Bacterial Infection		Cardiovascular events		Decompensation		Overall death	
Variables	**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
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;2N]	2.15 [1.27; 3.64]	.004					1.76 [1.01; 3.05]	.045	2.43 [1.42; 4.14]	.001
> 2N	2.38 [1.45; 3.89]	.001					2.56 [1.55; 4.22]	< .001	2.04 [1.23; 3.39]	.006
Albumin (g/L)										
≤ 35			2.02 [1.30; 3.16]	.002	1.89 [1.12; 3.22]	.018	2.05 [1.43; 2.94]	< .001	2.36 [1.60; 3.49]	< .001
> 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										
Never										
Past										
Ongoing										
Past history of CV events					3.14 [1.93; 5.10]	< .001			1.76 [1.12; 2.77]	.014
Arterial hypertension					2.06 [1.35; 3.14]	.001				
Diabetes										
Beta-blockers 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	0.49 [0.29; 0.82]	.007	0.45 [0.29; 0.69]	< .001	0.42 [0.27; 0.67]	< .001

SVR: sustained virological response; GFR: glomerular filtration rate; CV: cardiovascular

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

[b] Included as a time-dependent variable.

[c] Because of the low rates of patients declaring active alcohol intake at inclusion, only past excessive alcohol consumption according to WHO criteria was considered.

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).

	Extrahepatic cancer		MACE	
Variables	**HR [95% CI]**	**P**	**HR [95% CI]**	**P**
Age[a]	1.04 [1.01; 1.06]	.001		
Platelet count (10^3/mm^3)				
<100				
[100;150]				
> 150				
GGT levels				
≤ N				
]N;2N]				
> 2N				
Albumin (g/L)			2.27 [1.19; 4.32]	.013
≤ 35			Ref	
> 35				
GFR (MDRD formula)				
Past excessive alcohol consumption				
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			3.29 [1.82; 5.95]	< .001
Arterial hypertension			2.27 [1.36; 3.78]	.002
Diabetes				
Beta-blockers intake[b]				
Esophageal varices				
SVR[b]	1.63 [1.04; 2.57]	.035	0.53 [0.29; 0.97]	.039

SVR: sustained virological response; GFR: glomerular filtration rate; CV: cardiovascular

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

[b] Included as a time-dependent variable.

[c] Because of the low rates of patients declaring active alcohol intake at inclusion, only past excessive alcohol consumption according to WHO criteria was considered.

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) (continued).

	HCC		Bacterial Infection		Cardiovascular events		Decompensation		Overall death	
Variables	**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;2N]	2.16 [1.05; 4.44]	.036								
> 2N	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										
> 17										
Tobacco consumption						.010				
Never					Ref					
Past					1.11 [0.50; 2.49]	.80				
Ongoing					2.49 [1.33; 4.69]	.005				
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				
Arterial hypertension					3.37 [1.87; 6.09]	< .001				
Diabetes										
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

SVR: sustained virological response; CV: cardiovascular

[a] Age was studied as a categorical variable: Age > 50 years for Cox models analysing HCC and bacterial infection occurrence, age > 60 years for Cox model analysing decompensation occurrence. For the Cox models analysing 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 (n=630 patients, results of multivariate analyses).

	Extrahepatic cancer		MACE	
Variables	**HR [95% CI]**	**P**	**HR [95% CI]**	**P**
Age[a]				
Platelet count (10^3/mm^3)				
<100				
[100;150]				
> 150				
GGT levels				
≤ N				
]N;2N]				
> 2N				
Albumin (g/L)				
≤ 35				
> 35				
Total bilirubin (µmol/L)				
≤ 17			Ref	
> 17			2.03 [1.05 ; 3.93]	.036
Tobacco consumption				.025
Never			Ref	
Past			1.75 [0.74 ; 4.12]	.20
Ongoing			2.92 [1.35 ; 6.34]	.007
Substance or drug abuse				
Never				
Past				
Ongoing				
Past history of CV events			3.54 [1.57 ; 7.99]	.002
Arterial hypertension			2.88 [1.49 ; 5.56]	.002
Diabetes	2.12 [1.03 ; 4.35]	.042		
Dyslipidemia				
Esophageal varices				
Past history of malignancy				
SVR[b]				

SVR: sustained virological response; CV: cardiovascular

[a] Age was studied as a categorical variable: Age > 50 years for Cox models analysing HCC and bacterial infection occurrence, age > 60 years for Cox model analysing decompensation occurrence. For the Cox models analysing 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 (n=630 patients, results of multivariate analyses) (continued).

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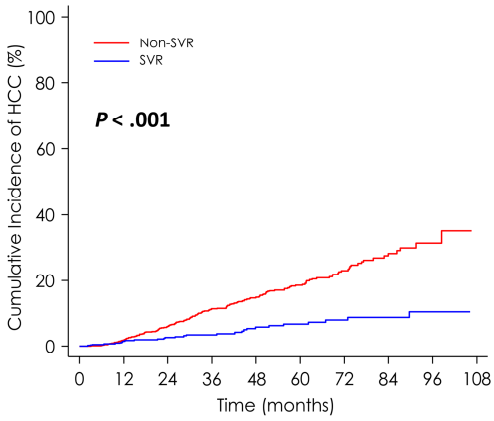

	Number at risk (events)																			
Non-SVR	1033	(17)	866	(34)	731	(38)	562	(20)	447	(17)	311	(14)	192	(10)	99	(3)	26	(1)	2
SVR	653	(8)	483	(5)	381	(3)	296	(6)	221	(2)	174	(2)	123	(1)	73	(1)	30	(0)	3

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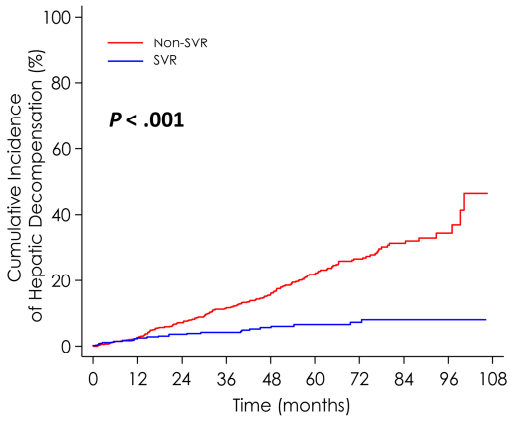
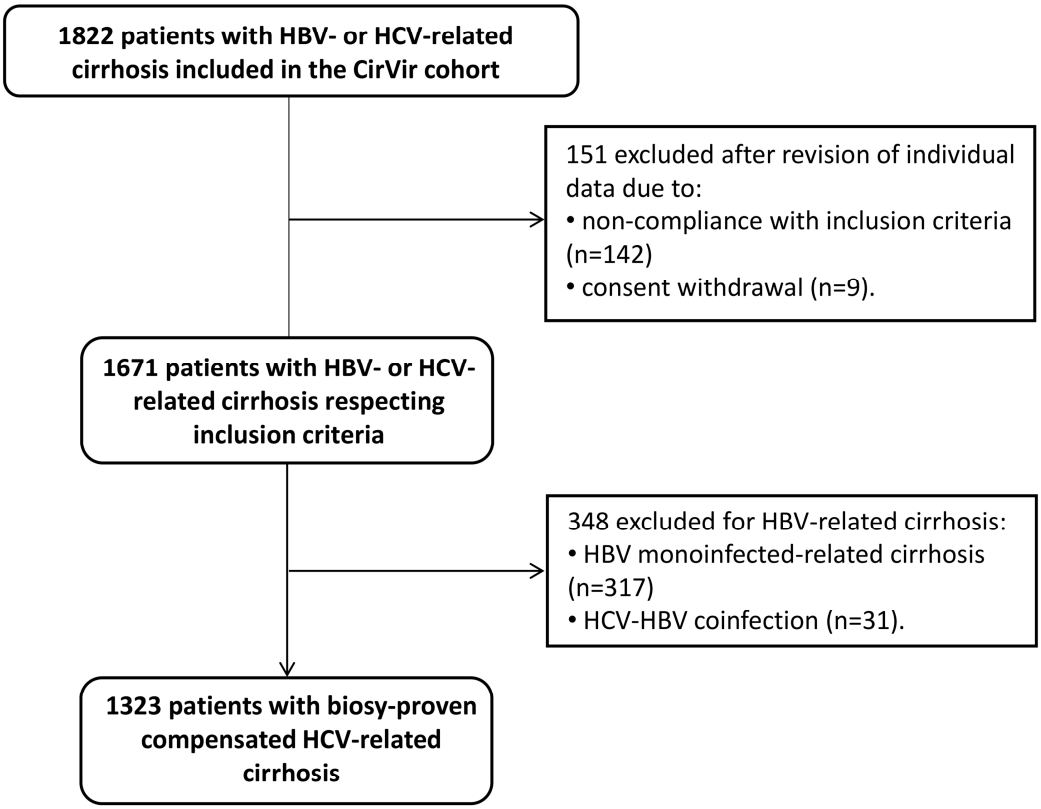


	Number at risk (events)																			
Non-SVR	1032	(25)	859	(38)	722	(31)	574	(26)	448	(27)	301	(16)	189	(10)	104	(3)	28	(3)	2
SVR	645	(14)	474	(5)	373	(2)	292	(4)	223	(2)	173	(1)	124	(1)	75	(0)	31	(0)	3



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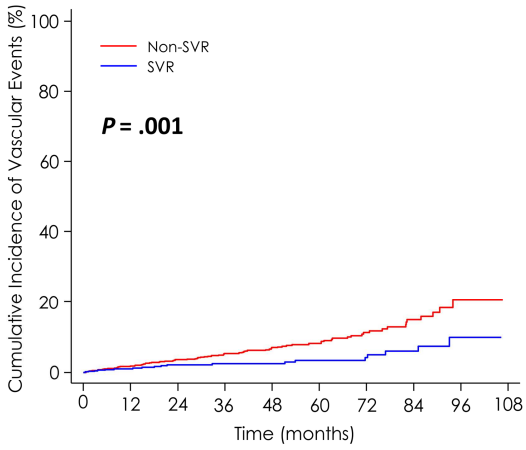
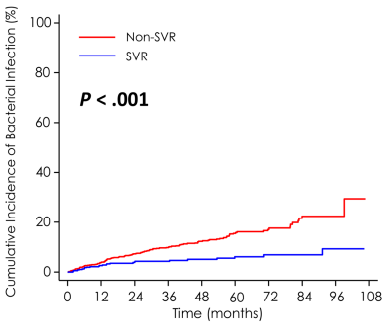


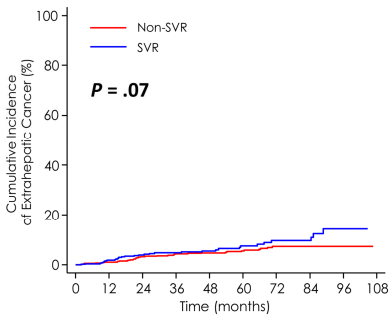
	Number at risk (events)
Non-SVR	1030(17) 863 (15) 742 (12) 599 (9) 469 (5) 324 (9) 199 (6) 109 (4) 29 (0) 2
SVR	655 (6) 479 (5) 377 (1) 291 (0) 221 (2) 169 (1) 120 (2) 72 (2) 29 (0) 3

B

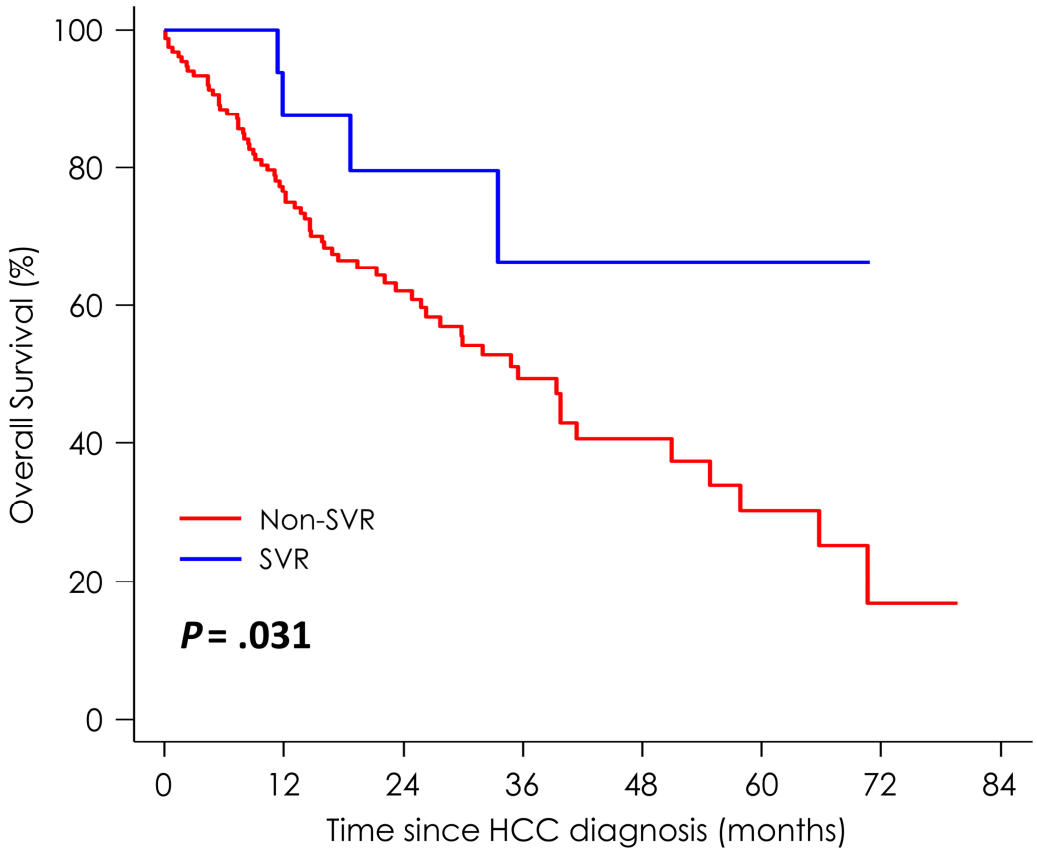


	Number at risk (events)
Non-SVR	1031 (37) 829 (27) 680 (17) 530 (13) 408 (12) 271 (4) 168 (7) 88 (0) 23 (1) 2
SVR	611 (14) 440 (5) 351 (2) 276 (2) 210 (2) 161 (1) 114 (0) 68 (1) 28 (0) 3

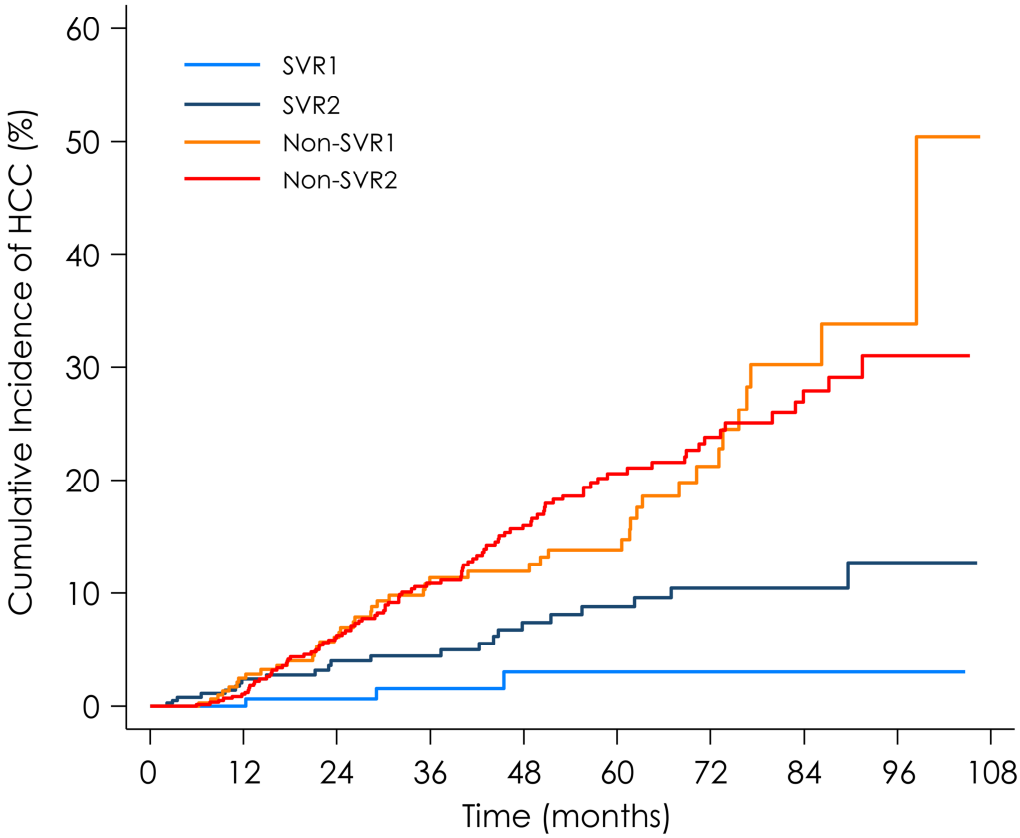
C



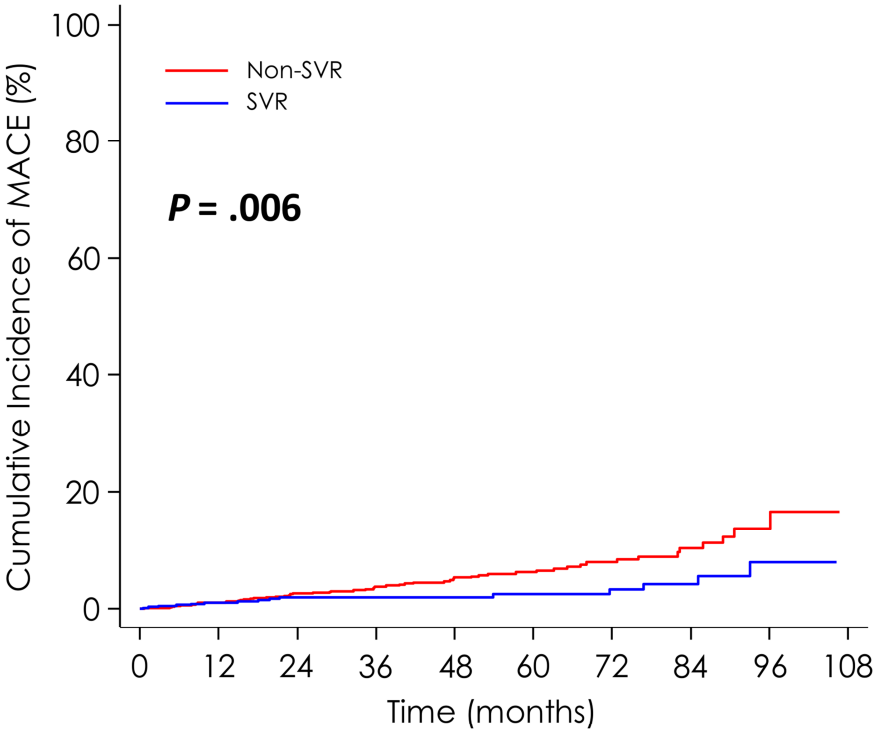
	Number at risk (events)
Non-SVR	1033 (10) 871 (17) 747 (8) 602 (2) 477 (3) 332 (5) 206 (0) 114 (0) 31 (0) 3
SVR	662 (10) 481 (9) 372 (3) 286 (2) 215 (4) 165 (3) 115 (0) 69 (3) 25 (0) 3



	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

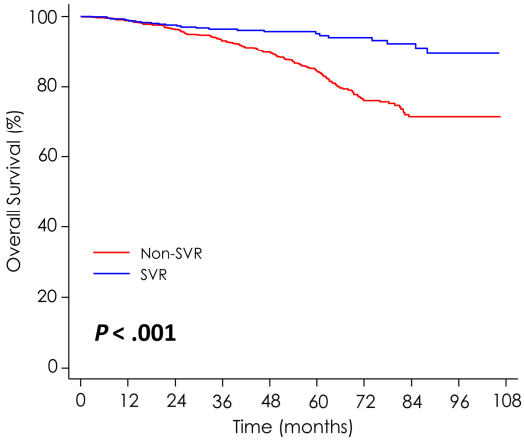


	Number at risk (events)																			
SVR1	208	(0)	152	(1)	118	(1)	89	(1)	59	(0)	40	(0)	25	(0)	15	(0)	8	(0)	2
SVR2	378	(8)	289	(4)	230	(1)	186	(5)	147	(2)	121	(2)	91	(0)	56	(1)	22	(0)	1
Non-SVR1	316	(7)	264	(9)	214	(11)	172	(1)	142	(3)	100	(7)	53	(5)	22	(1)	5	(1)	0
Non-SVR2	624	(6)	524	(25)	447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



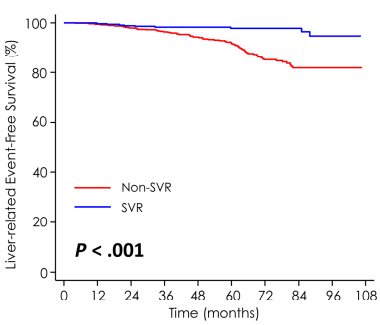
	Number at risk (events)																	
Non-SVR	1014	(9)	857	(13)	737	(8)	597	(8)	468	(4)	328	(5)	204	(4)	115	(3)	31	(1)	2
SVR	657	(6)	479	(4)	377	(0)	292	(0)	222	(1)	171	(1)	121	(1)	75	(2)	31	(0)	3

A



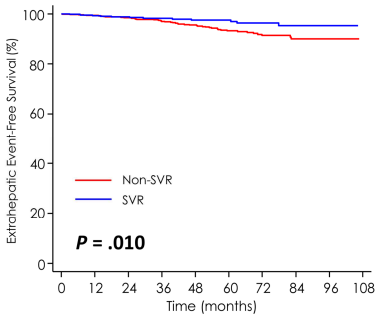
	Number at risk (events)
Non-SVR	1029(11) 877 (20) 765 (24) 622 (20) 496 (26) 349 (29) 220 (9) 122 (0) 33 (0) 3
SVR	667 (6) 492 (6) 389 (4) 303 (2) 230 (1) 180 (2) 129 (2) 78 (2) 32 (0) 3

B



	Number at risk (events)
Non-SVR	1014 (5) 863 (12) 752 (11) 612 (12) 486 (11) 344 (21) 218 (6) 122 (0) 33 (0) 3
SVR	665 (1) 491 (4) 388 (2) 302 (0) 229 (1) 179 (0) 128 (0) 78 (2) 32 (0) 3

C



	Number at risk (events)
Non-SVR	1014 (5) 863 (8) 752 (10) 612 (8) 486 (10) 344 (5) 218 (2) 122 (0) 33 (0) 3
SVR	665 (4) 491 (2) 388 (2) 302 (2) 229 (0) 179 (2) 128 (1) 78 (0) 32 (0) 3