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Viral Hepatitis

Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication

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Background & Aims: The risk of hepatocellular carcinoma (HCC) is reduced but not eradicated among patients with hepatitis C virus (HCV)-induced advanced hepatic fibrosis who attained sustained viral response (SVR). We aimed to assess the risk of cirrhosis-related complications in this specific group of patients.
Methods: Data from previously reported Western cohort studies including patients with chronic HCV infection and bridging fibrosis or cirrhosis who attained SVR were pooled for survival analyses on the individual patient level. The primary endpoint was HCC and the secondary endpoint was clinical disease progression, defined as liver failure, HCC or death.
Results: Included were 1000 patients with SVR. Median age was 52.7 (IQR 45.1–59.7) years, 676 (68%) were male and 842 (85%) had cirrhosis. Median follow-up was 5.7 (IQR 2.9–8.0) years. Fifty-one patients developed HCC and 101 had clinical disease progression. The cumulative 8-year HCC incidence was 1.8 (95% CI 0.0–4.3) among patients with bridging fibrosis and 8.7% (95% CI 6.0–11.4) among those with cirrhosis ($p = 0.058$). Within the cirrhosis group, the 8-year HCC incidence was 2.6% (95% CI 0.0–5.5) among patients <45 years, 9.7% (95% CI 5.8–13.6) among patients from 45–60 years, and 12.2% (95% CI 5.3–19.1) among patients >60 years of age at start of therapy ($p = 0.006$). Multivariable Cox analyses indicated that higher age, lower platelet count and diabetes mellitus were independently associated with development of HCC. After 8 years 4.2% (95% CI 0.1–8.3) of patients with bridging fibrosis and 15.8% (95% CI 12.3–19.3) of patients with cirrhosis experienced clinical disease progression ($p = 0.007$).
Conclusions: Patients with HCV-induced cirrhosis and SVR showed an annual risk of approximately 1% for HCC and 2% for clinical disease progression. Therefore, to prevent HCC surveillance, chronic HCV infection should preferably be treated before cirrhosis has developed.
Lay summary: Patients with cirrhosis who were able to eradicate their chronic HCV infection remain at substantial risk of primary liver cancer. The risk of liver cancer increases with higher age, laboratory makers suggesting more severe liver disease, and presence of diabetes mellitus. Also after successful antiviral therapy patients with HCV-induced cirrhosis should thus remain included in follow-up for early detection of liver cancer.

Keywords: Chronic hepatitis C; Cirrhosis; Sustained virological response; Hepatocellular carcinoma; Survival analysis; Fibrosis; Liver failure.
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Introduction

Chronic infection with the hepatitis C virus (HCV) may lead to the development of hepatic fibrosis, which can ultimately progress to cirrhosis. Patients with cirrhosis have an increased risk to develop end-stage liver disease and hepatocellular carcinoma (HCC) [1]. A recent meta-analysis found that chronic HCV-infected patients with advanced hepatic fibrosis had an overall annual risk of 2.9% to experience liver failure, 3.2% to develop HCC and 2.7% to die

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of liver-related causes [2]. According to the current guidelines these patients should be included in HCC surveillance programs [3,4]. In the forthcoming years, there will be an increase in the incidence of HCV-induced cirrhosis and its clinical complications in the Western world [5,6]. In fact, in the USA it is estimated that by 2030 almost half of the population with chronic HCV infection will have cirrhosis [5].

Antiviral therapy has been available since the early 1990s and is usually considered successful when a sustained virological response (SVR), defined as HCV RNA negativity 12 or 24 weeks after cessation of treatment, is attained. However, SVR rates have been disappointing with the interferon (IFN)-based regimens, especially among patients with advanced liver disease [7]. Even for this important subgroup of patients, however, the efficacy of antiviral therapy has improved tremendously due to the development of direct-acting antiviral drugs. Recently, various IFN-free regimens have actually showed cure rates well over 90 percent among patients with chronic HCV infection and bridging fibrosis or cirrhosis. Another advantage of these new treatment regimens concerns the good safety-profile, which should lead to an increase in treatment uptake. In the end, treating more patients is essential if we really want to reduce HCV-related morbidity and mortality [8]. Institution of HCV screening programs, such as birth-cohort screening in the USA, should therefore be considered as a major accomplishment as well [9,10].

Both the antiviral treatment improvements and implementation of screening for HCV infection are likely to increase the population with HCV-induced cirrhosis and SVR. Several studies have shown that the incidence of liver failure and HCC is markedly lower among patients with cirrhosis and SVR as compared to those without SVR [11–15]. However, these studies also indicated that the risk of HCC was not entirely eradicated even when the HCV infection was cured. Case reports have even described patients who were diagnosed with HCC up to 13 years following successful antiviral therapy [16]. To date, risk factors of HCC following SVR are largely unknown. Despite respectable follow-up durations, prior Western cohort studies did not include sufficient patients with SVR and HCC for subgroup analyses. This can be attributed to the low rate of SVR with IFN-based regimens among patients with cirrhosis as well as the low risk of cirrhosis-related complications following HCV eradication.

Here we present the results of a study which aimed to assess the risk of HCC, as well as liver disease progression in general, among Western patients with chronic HCV infection and advanced hepatic fibrosis following achievement of SVR. We also studied the baseline factors which were associated with these outcomes in this specific population.

Patients and methods

The primary investigators of previously reported European and Canadian-based cohort studies including patients with chronic HCV infection and advanced hepatic fibrosis were invited to participate in the current study based on individual patient data [11,12,14,15,17–24]. All patients with bridging fibrosis or cirrhosis were eligible for inclusion if they had attained SVR with an IFN-based antiviral treatment regimen and if there was available follow-up data. Patients co-infected with human immunodeficiency virus or hepatitis B virus were excluded.

The datasets of the original retrospective cohort studies based on chart review were sent to a single investigator (AJM), who monitored and entered the data into a uniform database system. In case of any doubt regarding the variables in the original dataset, the principal investigator of the participating cohort was contacted to answer any queries before incorporating the data into the central database.

We collected all available information on patient demographics (sex, age, body mass index [BMI]), stage of liver disease (bridging fibrosis or cirrhosis), antiviral treatment (type of IFN used), presence of diabetes mellitus (DM), a history of severe alcohol use, virology (HCV genotype, anti-hepatitis B core antigen [antiHBc] status) and start-of-treatment laboratory parameters (platelet count, bilirubin, albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase [gGT]). Cirrhosis was determined by either histopathological assessment of liver biopsy, transient elastography, or clinical judgement at the discretion of the treating physician based on a combination of biochemical parameters, clinical signs of portal hypertension and/or radiologic findings consistent with cirrhosis.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. All original study protocols had been reviewed and approved by the local ethics committees, and the results of all these studies have been published in the international literature. Informed consent had previously been obtained according to the local regulations of the participating centers in the original cohort studies.

Clinical events

The primary outcome of the study was development of HCC. Clinical disease progression was the secondary endpoint, which was defined as the occurrence of either HCC, liver failure, liver transplantation or mortality. In case multiple events occurred in a single subject, only the first event contributed to this combined clinical outcome measure.

In accordance with international guidelines, the diagnosis of HCC was based on histopathological confirmation or two coincident imaging techniques (computed tomography, magnetic resonance imaging or contrast-enhanced ultrasonography) showing a focal lesion larger than 2 cm with arterial-phase hyper enhancement or one imaging technique showing a focal lesion larger than 2 cm with arterial-phase hyper enhancement in the presence of an α-fetoprotein level greater than 400 ng/ml [25]. Liver failure was defined as an episode of either ascites, bleeding varices, jaundice or hepatic encephalopathy. Death was classified as liver-related or not liver-related. In general, death is considered liver-related in case this is due to end-stage HCC or because of deteriorating liver function, but was at the discretion of the treating physician who collected the data.

Statistical analysis

Follow-up started 24 weeks after the end-of-treatment, which was defined as time 0, since patients with undetectable HCV RNA at this time point were classified as having attained SVR. Patients who were diagnosed with HCC or patients who were lost to follow-up prior to 24 weeks after the end-of-treatment were not included in the analyses. In the survival analyses regarding clinical disease progression, patients who were diagnosed with HCC or who experienced liver failure prior to 24 week after the end-of-treatment were excluded. Patients were censored at their last date of follow-up.

The Kaplan-Meier method was used to assess the cumulative incidence of clinical events during follow-up, and differences according to categorical variables were assessed by the log-rank test. Univariable and multivariable Cox regression analyses were performed to assess which baseline variables were associated with the occurrence of clinical events. The proportionality assumption was checked by assessing if the effect of the variables on the outcome was changing over the log-transformed follow-up time for both continuous and categorical variables. Our multivariable models were constructed by considering all variables with a p value <0.1 in univariable analysis in a stepwise backward selection approach. Hereafter the variables outside of the model were introduced one-by-one to assess for possible confounding. The decision to keep the AST/ALT ratio in the model for HCC was made afterwards because of the borderline statistical significance, the effect size, and the biological plausibility of the association. As the period of inclusion was rather long, the analyses were stratified for the median year of inclusion. Adjustment for the type of IFN was considered as the chance of SVR is higher with pegylated (Peg)IFN as opposed to IFN. Because the hazard ratios of the variables in the model for HCC did hardly change by inclusion of the type of IFN, while this did result in overparameterization due to the limited number of HCC events, we decided to refrain from adjusting for type of IFN in the analyses of HCC.

The primary analyses concerned complete-case analyses. As a result of differences in data collection among the participating cohort studies, entire cohorts could drop out of the multivariable analyses in case the included baseline variables were not available. As sensitivity analyses, multiple imputation to impute missing values was performed with the iterative random number-based Markov Chain Monte Carlo method assuming multivariate normality with

non-informative prior to using the SAS Proc MI package, by which 10 complete datasets were constructed in order to check the stability of the final multivariable Cox regression models.

All statistical tests were two-sided, and a p value <0.05 was considered to be statistically significant. The significance level for interactions was set at $p = 0.01$ to correct for multiple testing. SPSS version 22.0.1 (SPSS Inc., Chicago, IL, USA) and SAS 9.3 PROC GENMOD (SAS institute, Cary, NC, USA) were used for all statistical analyses.

Results

Study population

In total, 1000 patients with advanced hepatic fibrosis who had attained SVR were analysed from previously reported HCV treatment cohorts with long-term follow-up [11,12,14,15,17–24] (Supplementary Table 1). The median age was 52.7 years (interquartile range [IQR] 45.1–59.7) and 676 (68%) patients were male. Cirrhosis was present in 842 (85%) patients, others were classified as having bridging fibrosis. The stage of liver disease was based on liver histology in 896 (90%) patients and on transient elastography, presence of esophageal varices, and/or clinical judgement in 83 (8%) patients. For 21 (2%) patients data regarding the diagnostic modality on which the stage of liver disease was based was not available. Table 1 describes all baseline variables. The majority of patients were treated with a PegIFN-based regimen (n = 701, 70%). In five (<1%) patients a protease inhibitor was added. The year that successful antiviral therapy was initiated ranged from 1987 to 2010 (median 2002 [IQR 1999–2005]). Patients were followed for a median duration of 5.7 years (IQR 2.9–8.0).

Hepatocellular carcinoma

During follow-up, 51 patients were diagnosed with HCC, which resulted in a HCC rate of 0.90 per 100 person-years (95% confidence interval [CI] 0.67–1.18) (Table 2). The time interval between SVR and the diagnosis of HCC ranged from 0.2 to 11.8 years (median 5.8 years, IQR 2.6–7.4). The median age at the time of HCC was 65 years (IQR 57–69). The overall cumulative 8-year HCC incidence was 7.6% (95% CI 5.2–10.0). The cumulative 8-year HCC incidence was markedly higher among patients with cirrhosis (8.7%, 95% CI 6.0–11.4) as compared to patients who were classified as having bridging fibrosis (1.8%, 95% CI 0.0–4.3) (Fig. 1). Among patients with cirrhosis, those below the age of 45 at the start of therapy showed a cumulative 8-year HCC rate of 2.6% (95% CI 0.0–5.5), while this was 12.2% (95% CI 5.3–19.1) among patients above 60 years of age (Fig. 2). Three of the 158 (2%) patients classified as having bridging fibrosis were diagnosed with HCC after 3.1, 3.9 and 9.8 years following achievement of SVR. All were around 60 years of age at the start of therapy. None had DM at baseline and their BMI ranged from 23.3 to 25.8. The first two patients had no history of alcohol abuse, but data on alcohol use was not available for the third patient. Their baseline platelets ranged from 127 to 166 $\times 10^9$/L.

Table 3 shows the results of the Cox regression analyses regarding HCC occurrence among the total group of patients. Significantly associated with HCC in univariable analyses were higher age, lower platelet count, higher AST/ALT ratio, and prior unsuccessful antiviral therapy. Gender did not influence the risk of HCC ($p = 0.426$). In multivariable analyses, the platelet count remained an independent predictor of HCC. Although the HR of the AST/ALT ratio (HR 1.04, 95% CI 1.00–1.09, $p = 0.084$) remained similar to that in univariable analysis, the association between the AST/ALT ratio and HCC fell just outside of the pre-specified significance level in the multivariable Cox model. Adjusted for age and the laboratory markers of liver disease severity, the association between DM was statistically significant (HR 2.36, 95% CI 1.02–5.42, $p = 0.044$). When added to the final model, being treatment naïve was no longer significantly associated with HCC (HR 0.71, 95% CI 0.34–1.48, $p = 0.363$). The proportional hazard assumptions were met and there were no statistically significant interactions between the variables included in the final model. Following imputation of missing data, which was performed as a sensitivity analysis, the estimated HRs were similar (Table 3).

Table 1. Baseline characteristics.[*]

	Overall (n = 1000)
Age, years, median (IQR)[#]	52.7 (45.1–59.7)
<45 years	241/998 (24)
45–60 years	526/998 (53)
>60 years	231/998 (23)
Males	676/1000 (68)
BMI, kg/m^2, median (IQR)[¥]	25.7 (23.3–28.4)
BMI >28	211/752 (28.1)
Disease stage	
Bridging fibrosis	153/995 (15)
Cirrhosis	842/995 (85)
HCV genotype	
1	459/918 (50)
2	220/918 (24)
3	181/918 (20)
4	49/918 (5)
Other	9/918 (1)
Type of treatment	
IFN (± ribavirin)	294/997 (30)
PegIFN (± ribavirin)	701/997 (70)
consensus IFN (+ ribavirin)	2/997 (<1)
Laboratory markers of liver disease severity, median (IQR)[£]	
Platelet count, $\times 10^9$/L	150 (116–194)
Albumin, g/L	42 (39–44)
Bilirubin, mmol/L	13.7 (10.3–17.1)
AST/ALT ratio	0.72 (0.57–0.90)
gGT, IU/L	56 (34–98)
Treatment naïve, n/of total (%)	624/972 (64)
Year treatment started[≠]	2002 (1999–2005)
Diabetes mellitus, n/of total (%)	117/819 (14)
History of severe alcohol use, n/of total (%)	128/575 (22)
AntiHBc positive, n/of total (%)	198/643 (31)

ALT, Alanine aminotransferase; antiHBc, anti-hepatitis B core antigen; AST, aspartate aminotransferase; BMI, body mass index; gGT, gamma-glutamyltransferase; HCV, hepatitis C virus; IQR, interquartile range; IFN, interferon; PegIFN, pegylated interferon.

[*]Data are presented as No./Total No. (%) unless otherwise noted.

[#]Age was available in 998 (~100%) patients.

[¥]BMI was available in 642 (64%) patients. One of the participating cohorts had collected data on BMI as a categorical variable (BMI ⩽28 kg/m^2 or >28 kg/m^2), so that more data was available when BMI was categorized according to the 28 kg/m^2 cut-off.

[£]Platelet count was available in 955 (96%) patients, albumin in 808 (81%) patients, bilirubin in 813 (81%) patients, AST/ALT ratio in 801 (80%) patients and gGT in 700 (70%) patients.

[≠]The year treatment started was available in 991 (99%) patients.

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Table 2. Event rate per 100 person-years.

	Events No.	Observation period, person-years	Rate/100 person-years (95% CI)
Hepatocellular carcinoma	51	5671	0.90 (0.67–1.18)
Liver failure	26	5664	0.46 (0.30–0.67)
All-cause mortality	56	5750	0.97 (0.74–1.26)
Clinical disease progression	101	5592	1.80 (1.47–2.20)

CI; confidence interval.

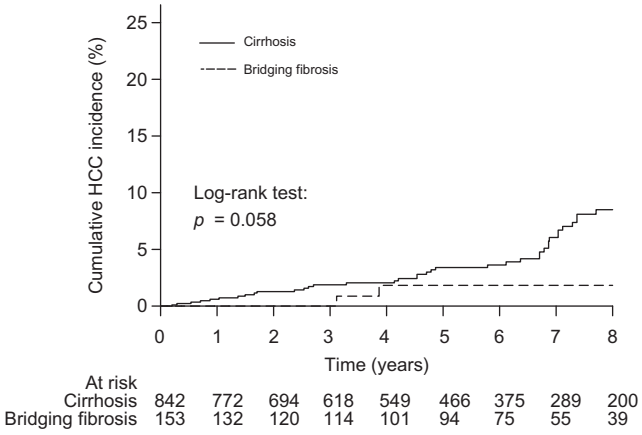

Fig. 1. Incidence of hepatocellular carcinoma following sustained virological response according to the presence of bridging fibrosis or cirrhosis. Kaplan-Meier graph for the cumulative incidence of hepatocellular carcinoma (HCC) according to the presence of bridging fibrosis or cirrhosis. The *p* value is based on the log-rank test.

Clinical disease progression

In nine patients, liver failure occurred either before the start of therapy (n = 3), during therapy (n = 1) or after therapy but prior to achievement of SVR (n = 5). After exclusion of these patients, 26 of the 991 remaining patients experienced liver failure during follow-up (Table 2). Ascites was most frequently observed (n = 13, 50.0%), followed by variceal bleeding (n = 7, 26.9%), hepatic encephalopathy (n = 2, 7.7%) and jaundice (n = 1, 3.8%). Three (11.5%) patients had either ascites and/or encephalopathy, as detailed data on the specific event was not available. None of the patients with bridging fibrosis experienced liver failure. Among patients with cirrhosis, the 8-year cumulative incidence of liver failure was 4.1% (95% CI 2.3–5.9) (Fig. 3A). In three (11.5%) of the patients with liver failure, the event occurred within 6 months of the diagnosis of HCC or thereafter. Three patients, all with HCC, underwent liver transplantation. During the follow-up 56 (5.6%) patients died, which was registered to be due to liver-related causes in 24 (42.8%) patients and due to other causes in 25 (44.6%) patients (Table 2). For 7 (12.5%) patients the cause of death was not known. The cumulative 8-year all-cause mortality rate was 3.3% (95% CI 0.0–7.0) among patients with bridging fibrosis *vs.* 9.6% (95% CI 6.7–12.5) among patients with cirrhosis at baseline (Fig. 3B).

In total, 101 (10.2%) patients showed clinical progression of their liver disease, resulting in a clinical disease progression rate of 1.80 per 100 person-years (95% CI 1.47–2.20) (Table 2). The first event was HCC in 47 (46.5%) patients, liver failure in 24 (23.8%) patients and death in 30 (29.7%) patients. The overall cumulative 8-year clinical disease progression rate was 14.0% (95% CI 11.1–16.9), which differed significantly among patients with bridging fibrosis (4.2, 95% CI 0.1–8.3) as compared to patients with cirrhosis (15.8, 95% CI 12.3–19.3) (Fig. 3C). Again, patients with cirrhosis below the age of 45 at the start of successful antiviral therapy showed a statistically significantly lower incidence of events at 8 years of follow-up (7.9, 95% CI 2.4–13.4) as compared to those between 45 and 65 years of age (17.1, 95% CI 12.2–22.0) or those above the age of 65 (20.7, 95% CI 12.3–29.1).

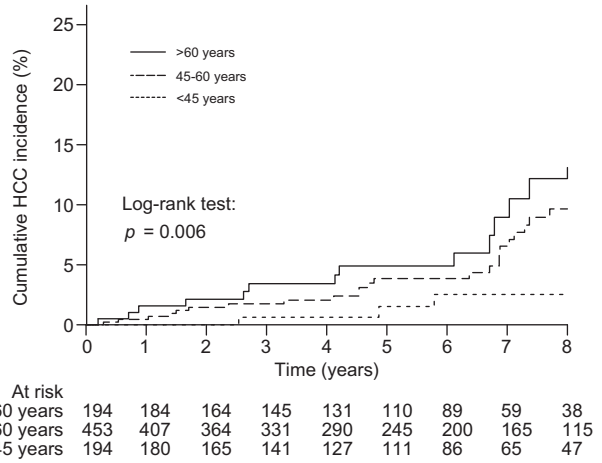

Fig. 2. Incidence of hepatocellular carcinoma following sustained virological response according to age among patients with cirrhosis. The incidence curves for hepatocellular carcinoma (HCC) were constructed using the Kaplan-Meier method. Twenty-four weeks after cessation of antiviral therapy was considered as time 0. Statistical significance was assessed with the log-rank test.

Cox regression analysis indicated that higher age, cirrhosis, lower platelet counts, and lower albumin levels were independently and significantly associated with clinical disease progression (Table 4). The associations between the variables and clinical disease progression were proportional over time, and there were no statistically significant interactions among the variables included in the final model. The final multivariable Cox regression model showed similar results in the imputation analyses.

Discussion

This is the first Western study among patients with chronic HCV infection and advanced liver disease to assess the risk of cirrhosis-related complications following achievement of SVR. We found that the annual risk of HCC among patients with cirrhosis who cleared their HCV infection with IFN-based antiviral therapy was almost 1%. The annual risk of cirrhosis-related morbidity or mortality, as a combined endpoint, was twice as high. The complications of advanced liver disease were more frequently observed among patients who were older at the start of successful antiviral therapy and among patients with more severe liver disease. As was previously described for patients with cirrhosis and ongoing HCV infection, DM was an independent risk factor for HCC following SVR as well [26].

Since the HCV-infected population is aging and the proportion of patients with more advanced liver disease is increasing, our

Table 3. Cox proportional hazard analyses for hepatocellular carcinoma.

	Hepatocellular carcinoma								
	Univariable analyses			Multivariable analyses (n = 630)[#]			Imputation analyses (n = 1000)[#]		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age									
<45 years	1.00	Ref.	Ref.	1.00	Ref.	Ref.	1.00	Ref.	Ref.
45–60 years	5.13	1.57–16.79	0.007	8.54	1.13–64.64	0.038	9.68	1.28–72.95	0.028
>60 years	6.95	2.03–23.76	0.002	8.91	1.12–70.79	0.039	9.76	1.23–77.77	0.031
Males	1.28	0.69–2.38	0.426	-	-	-	-	-	-
BMI, per 1.0 kg/m^2	1.03	0.96–1.13	0.314	-	-	-	-	-	-
Cirrhosis	2.94	0.91–9.42	0.071	-	-	-	-	-	-
Laboratory markers of liver disease severity									
Platelet count, per 10 × 10^9/L	0.93	0.88–0.98	0.005	0.94	0.87–1.00	0.048	0.93	0.87–0.99	0.029
Bilirubin, per mmol/L	1.01	0.99–1.04	0.233	-	-	-	-	-	-
Albumin, per g/L	0.97	0.91–1.04	0.428	-	-	-	-	-	-
AST/ALT ratio, per 0.1	1.04	1.00–1.08	0.046	1.04	1.00–1.09	0.084	1.04	1.00–1.09	0.068
gGT, per 10 IU/L	1.02	0.99–1.04	0.143	-	-	-	-	-	-
Treatment naïve	0.39	0.22–0.71	0.002	-	-	-	-	-	-
Diabetes mellitus	1.90	0.91–4.00	0.090	2.36	1.02–5.42	0.044	2.27	0.98–5.29	0.057
History of severe alcohol use	0.89	0.40–1.97	0.774	-	-	-	-	-	-
Anti-HBc positive	1.16	0.60–2.25	0.655	-	-	-	-	-	-

BMI, body mass index; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; gGT, gamma-glutamyltransferase; antiHBc, anti-hepatitis B core antigen.

[#] The multivariable models were stratified by the median year of inclusion (2002).

results suggest that we will more frequently encounter HCC, liver failure and liver-related mortality among patients with cured HCV infection in the following years [5]. Although cirrhosis was not statistically significantly associated with HCC in our cohort, this is still likely to be an important risk factor. It is relevant to consider that not all participating cohorts included patients with bridging fibrosis, so that a lack of power may be of influence here. The platelet count, which represents the extent of liver damage and portal pressure, was significantly associated with HCC. Even though the AST/ALT ratio fell just outside of the predefined α-level in multivariable analyses, this readily available non-invasive marker of hepatic fibrosis showed a strong trend for a clinically relevant effect size. For this reason we kept the AST/ALT ratio in our final model. The risk of clinical disease progression, of which more events could be registered, was statistically significantly higher in case of cirrhosis rather than bridging fibrosis. Regardless of the severity of the HCV-induced liver disease, the prevalence of insulin resistance is rapidly rising as well [27]. Despite accumulation of these unfavorable prognostic characteristics, improvements in antiviral therapy will enable us to cure more patients. In fact, various IFN-free regimens have been shown to cure approximately 95% of patients, whether or not cirrhosis is present [28–32]. Thus, it is highly relevant that physicians are aware of the continuing health risks following successful antiviral therapy among patients with HCV-induced advanced liver disease.

An important message of our study is that patients with HCV-related cirrhosis who have attained SVR should probably remain included in HCC surveillance programs. Current AASLD guidelines state that HCC surveillance is cost-effective in patients with hepatitis C if the annual risk exceeds 1.5% [3]. Although in our study the overall risk among patients with cirrhosis and SVR did not meet this cut-off, there are several reasons to justify why these patients should be followed. First, the risk of HCC increased with age and the population with cured HCV infection is rapidly aging. In fact, patients who initiated their successful antiviral treatment course above the age of 60 did meet the annual HCC risk cut-off of 1.5% as the HCC rate in this subgroup was 1.50 per 100 person-years (data not shown). For patients who were younger at the time of SVR it is possible that as they age the risk of HCC may actually increase. Second, with the current effective and safe IFN-free treatment regimens patients who are older and patients with more advanced liver disease can be cured. Our data showed that more advanced hepatic fibrosis (lower platelet count, higher AST/ALT ratio and lower albumin level) were pre-treatment predictors of cirrhosis-related events following SVR. Also, given the intrinsic antiproliferative properties of IFN, we cannot exclude that the incidence of HCC will be higher among patients who attained SVR with IFN-free regimens. Third, in case of SVR, the potential gain in life-years following the diagnosis of HCC may be higher due to reduced risk of other cirrhosis-related complications [11–13,15,33]. In a randomized controlled study among patients with compensated HCV-induced cirrhosis and HCC, Shiratori *et al.* found that the 7-year survival following tumor ablation was 53% among those treated with IFN *vs.* 23% among those not treated with IFN [34]. Within the IFN-treated group, the survival at 7 years of follow-up was higher among patients with SVR (68%) as compared to patients without SVR (47%). Similar results were described in a retrospective study, which also analysed hepatitis C patients with cirrhosis who underwent IFN-based therapy prior to HCC development [35]. In this study the cumulative survival was 93% among those with SVR and 57% among those without SVR at 6 years following HCC. Further studies are required to determine the annual HCC risk cut-off for cost-effective surveillance among patients with cirrhosis and SVR.

In our study three patients with bridging fibrosis and SVR were diagnosed with HCC. Among these patients there was no

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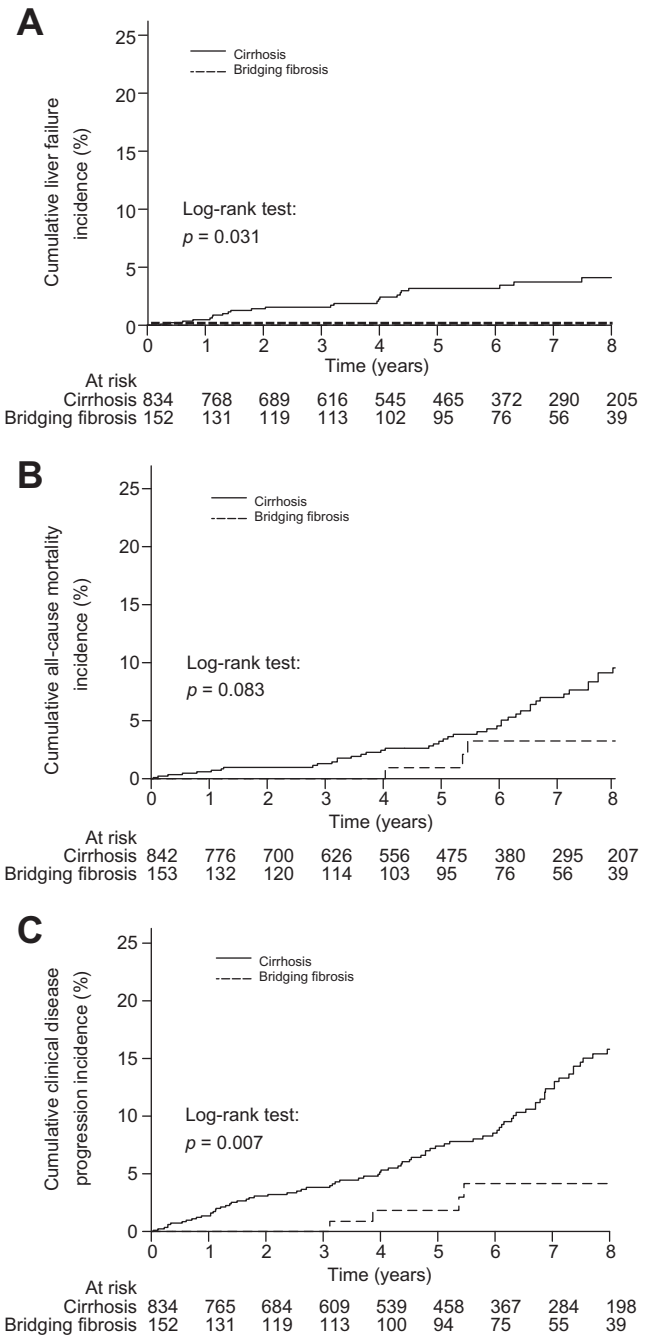

Fig. 3. Incidence of liver failure, all-cause mortality and clinical disease progression following sustained virological response according to the presence of bridging fibrosis or cirrhosis. The incidence curves for liver failure (A), all-cause mortality (B) and clinical disease progression (C) were constructed using the Kaplan-Meier method. Clinical disease progression was defined as the occurrence of liver failure, hepatocellular carcinoma, liver transplantation or death. Twenty-four weeks after cessation of antiviral therapy was considered as time 0. Statistical significance was assessed with the log-rank test.

clear evidence for other causes of liver injury. In one patient, however, the interval between the pre-treatment liver biopsy and the initiation of antiviral therapy was rather long (3.8 years) so that progression to cirrhosis cannot be excluded. In fact, the platelet counts were low in all three patients, which might suggest underestimation of severity of liver disease due to sampling error [36]. Nevertheless, cases of HCC have been previously reported in Western patients with chronic HCV infection without cirrhosis following SVR [37]. Although it cannot be excluded that successfully treated patients with bridging fibrosis may develop HCC, their risk seems to be low. Before deciding to discharge the individual patient with bridging fibrosis and SVR from further follow-up, physicians should take secondary markers of liver disease severity into account to ensure that the patient had not progressed to cirrhosis since the pre-treatment hepatic fibrosis assessment.

Although this is the first study to assess the incidence of HCC among a large cohort of patients with HCV-induced advanced fibrosis and SVR, previous studies have evaluated risk factors of HCC following SVR. Yet, all these studies were performed in East Asia and included predominantly patients without advanced liver disease [38–46]. Still, the reported cumulative HCC incidences were relatively high, with 5-year rates ranging from 1.5 to approximately 6%. Advanced hepatic fibrosis was an important universal risk factor for development of HCC following SVR in these studies. In this subgroup the cumulative HCC incidence ranged from 9 to 15.6% after 5 years of follow-up. Genetic differences, the earlier wave of HCV infection, the higher prevalence of hepatitis B virus and a higher dietary exposure to alcohol or aflatoxin through *Aspergillus*-contaminated food products in Asia are possible explanations for this epidemiological difference in HCC occurrence between the East and the West [47,48]. Our study is novel as it specifically assesses the residual risk of HCC, its pattern of development over time and specific risk factors following SVR in the subgroup of patients with cirrhosis from the West. We found age, severity of liver disease and diabetes to be associated with HCC occurrence among patients with advanced liver disease and SVR.

It will probably remain difficult to accurately identify patients with cirrhosis and SVR who have a sufficiently low risk of HCC to be discharged from further follow-up. Pre-treatment predictors may not suffice as there are many factors following SVR which can influence a patient's risk. Even though the current data might suggest that patients with cirrhosis below the age of 45 may not require surveillance following SVR, it remains unknown whether their risk of HCC will increase as they age. Future studies need to assess the predictive accuracy of post-treatment markers and their kinetics during follow-up, as a recent study indicated that regression of hepatic fibrosis following antiviral therapy among patients with cirrhosis was associated with improved clinical outcome [21]. A history of alcohol abuse was not associated with HCC or clinical disease progression in the current cohort. Although we cannot exclude the possibility that heterogeneity of the gathered data or missing data may be partly responsible for these lacking associations, it should also be considered that all included patients underwent IFN-based therapy which is not generally administered to those with severe alcohol abuse. Data on alcohol use following successful antiviral therapy were not available in our cohort. It may be expected, however, that continuous alcohol abuse increases the risk of cirrhosis-related complications among patients with advanced liver disease and SVR as well, so that also these patients should be advised to limit their alcohol intake [49,50]. Non-alcoholic fatty liver disease or new hepatotrophic infectious agents also represent plausible causes of continuing hepatic inflammation which may drive

Table 4. Cox proportional hazard analyses for clinical disease progression.

	Clinical disease progression								
	Univariable analyses			Multivariable analyses (n = 785)[#]			Imputation analyses (n = 991)[#]		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age									
<45 years	1.00	Ref.	Ref.	1.00	Ref.	Ref.	1.00	Ref.	Ref.
45–60 years	2.68	1.41–5.12	0.003	1.81	0.87–3.76	0.112	2.08	1.08–4.01	0.028
>60 years	3.60	1.81–7.16	<0.001	2.54	1.17–5.49	0.018	2.75	1.37–5.55	0.005
Males	1.21	0.79–1.86	0.390	-	-	-	-	-	-
BMI, per 1.0 kg/m^2	1.02	0.96–1.09	0.465	-	-	-	-	-	-
Cirrhosis	2.94	1.29–6.73	0.010	2.99	1.05–8.51	0.040	2.78	1.17–6.63	0.021
Laboratory markers of liver disease severity									
Platelet count, per 10×10^9/L	0.92	0.89–0.96	<0.001	0.95	0.91–0.99	0.020	0.95	0.91–1.00	0.040
Bilirubin, per mmol/L	1.02	1.00–1.03	0.012	-	-	-	-	-	-
Albumin, per g/L	0.93	0.90–0.97	0.002	0.94	0.90–0.99	0.018	0.94	0.90–0.99	0.016
AST/ALT ratio, per 0.1	1.04	1.01–1.06	0.006	-	-	-	-	-	-
gGT, per 10 IU/L	1.02	1.00–1.03	0.079	-	-	-	-	-	-
Treatment naïve	0.71	0.47–1.07	0.050	-	-	-	-	-	-
Diabetes mellitus	1.60	0.94–2.72	0.085	-	-	-	-	-	-
History of severe alcohol use	0.80	0.44–1.45	0.464	-	-	-	-	-	-
AntiHBc positive	1.09	0.68–1.77	0.715	-	-	-	-	-	-

BMI, body mass index; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; gGT, gamma-glutamyltransferase; antiHBc, anti-hepatitis B core antigen.

[#] The multivariable models were stratified by the median year of inclusion (2002) and adjusted for the type of interferon.

carcinogenesis following HCV eradication. Future studies need to assess their contribution to the outcome of patients with SVR in more detail.

Because the clinical efficacy of antiviral therapy is highest among those with advanced liver disease, costly new treatment regimens are mostly limited to this subgroup which is at highest risk of cirrhosis-related events [51]. The data presented here actually suggest that we should pursue successful antiviral therapy prior to the stage of advanced fibrosis. This can save the costs of both HCC surveillance as well as the cirrhosis-related complications. It might thus be worthwhile not to neglect patients with lesser stages of hepatic fibrosis, especially those prone to progress to cirrhosis [52].

Our study has several limitations. As data were combined from previously published cohorts from multiple countries, some heterogeneity regarding the collected data could not be prevented. On the other hand, the participating cohort studies had rather similar inclusion and exclusion criteria and comparable follow-up designs. The fact that many countries are represented in this combined cohort makes the presented estimates applicable to a broad spectrum of patients as well. Still, databases differed and there was missing data for some variables. We have therefore performed imputation analyses to check the stability of the estimated hazard ratios. Methodological differences between the participating cohorts with respect to data collection were an important reason for missing data in our study, however, as not all cohorts registered all the variables which were included in our analyses. As a result, possible bias due to missing data which might not be missing at random may be limited. Unfortunately, data regarding the evolution of liver disease during follow-up or at the time of HCC were not available, which might be relevant in order to differentiate patients with SVR who remain at risk for the cirrhosis-related complication from those who are no longer at risk. Also, because the cohort studies that were part of this analysis had retrospective designs, it is possible that some events may have been missed. This would tend to bias our estimates to a lower rate of HCC, however, and thus only increase the need for ongoing surveillance. Finally, because all patients in this cohort were eligible to be treated with IFN-based therapy, the patients included here had advanced but clinically stable liver disease. While our data suggest that patients with more advanced cirrhosis prior to SVR are at higher risk of cirrhosis-related complications, future studies should assess the clinical outcome among those with Child-Pugh score B and C who are now successfully treated with the IFN-free regimens.

To conclude, patients with chronic HCV infection and advanced fibrosis who have attained SVR remain at risk of HCC and other cirrhosis-related complications. Preferably, patients should thus be cured of their HCV infection prior to the development of advanced hepatic fibrosis. In case this is not accomplished, it is important to consider continued HCC surveillance upon achievement of SVR.

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Conflict of interest

Dr. Colombo reports personal fees from Gilead Sciences, personal fees from AbbVie, personal fees from BMS, personal fees from Roche, personal fees from Bayer, personal fees from Vertex, personal fees from Merck, personal fees from Novartis, personal fees

from Janssen, personal fees from Sanofi, outside the submitted work. Dr. Aleman reports personal fees from Consultant fees for lectures from Gilead, Abbvie and BMS, personal fees from Consulting from Gilead, Abbvie, BMS, MSD, outside the submitted work. Dr. D'Ambrosio reports personal fees from Gilead, personal fees from AbbVie, personal fees from Merck, outside the submitted work. Dr. Feld reports grants and personal fees from AbbVie, grants and personal fees from Gilead Sciences, personal fees from Bristol Meiers Squibb (BMS), grants and personal fees from Janssen, grants and personal fees from Merck, grants from Abbott, outside the submitted work. Dr. Ganne-Carrié reports personal fees from GIlead, personal fees from BMS, outside the submitted work. Dr. Hofer reports personal fees (lecture fees, advisory board) from AbbVie, BMS, Gilead, Janssen, MSD and a research grant form AbbVie outside the submitted work. Dr. Maan reports personal fees from AbbVie, during the conduct of the study. Dr. Mallet reports personal fees and non-financial support from Gilead, personal fees from Abbvie, personal fees and nonfinancial support from MSD, personal fees and non-financial support from JJ/Janssen-Cilag, personal fees from Bristol Myers Squibb, personal fees from Novartis, personal fees from Roche, outside the submitted work. Dr. van der Meer reports personal fees from Gilead, personal fees from BMS, outside the submitted work.

All other authors have no conflicts of interest with respect to presented work.

Authors' contributions

All authors partook in study concept and design, acquisition of data and critical revision of the manuscript. Analysis and interpretation of data: A van der Meer, J Feld, B Hansen and H Janssen. Drafting of the manuscript: A van der Meer, J Feld, H Janssen. Statistical analyses: A van der Meer and B Hansen. Study supervision: A van der Meer and H Janssen.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.10.017.

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