

# A Risk for Hepatocellular Carcinoma Persists Long-term After Sustained Virologic Response in Patients With Hepatitis C–Associated Liver Cirrhosis

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(See the Editorial Commentary by Pereira and Feld on pages 237–9.)

**Background.** The long-term effect of sustained virologic response (SVR) to antiviral therapy on the risk of developing hepatocellular carcinoma (HCC), liver complications, liver-related death, and overall death in hepatitis C virus (HCV)–infected patients with liver cirrhosis is not fully known.

**Methods.** These risks were evaluated during long-term follow-up in 351 patients with HCV-related cirrhosis. One hundred ten patients with SVR, 193 with non-SVR, and 48 who were untreated were included in a multicenter cohort that was initiated in 2001 and prospectively followed up for a mean of 5.3 (SD, 2.8) years. Complementary follow-up data from national registries were used to minimize the loss of patients during follow-up.

**Results.** Six patients with SVR developed HCC at 0.04, 0.64, 2.4, 7.4, 7.4, and 7.6 years, respectively, after achieving SVR. The incidences of HCC, any liver complication, liver-related death, and overall death per 100 person-years were significantly lower in SVR time with 1.0, 0.9, 0.7, and 1.9, compared to 2.3, 3.2, 3.0, and 4.1 in non-SVR and 4.0, 4.9, 4.5, and 5.1 in untreated time. The long-term consequences did not decline significantly after >3 years versus during the first 3 years of follow-up.

**Conclusions.** The risk for HCC, liver decompensation, and death in patients with liver cirrhosis related to HCV was markedly reduced after SVR, but a long-term risk of developing HCC remains for up to 8 years. Cirrhotic patients with HCV who achieve SVR should therefore maintain long-term surveillance for HCC. Future studies aimed to better identify those with remaining long-term risk for HCC are needed.

**Keywords.** hepatocellular carcinoma; liver decompensation; liver-related death; complications; sustained virologic response.

Hepatitis C virus (HCV) infection is a major cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. Patients with liver cirrhosis have a higher risk of developing HCC than patients with less advanced fibrosis [1].

Hence, in cirrhotic patients, surveillance for HCC every 6 months by ultrasound is recommended [2].

Since the introduction of standard-of-care therapy with pegylated interferon (peg-IFN) and ribavirin (RBV), the rate of sustained virologic response (SVR) increased compared to earlier treatments and has further improved with the use of first-generation protease inhibitors [3–7]. Studies analyzing the impact of SVR on the risk for developing HCC, liver complications, and liver-related death in cirrhotic patients have included small numbers of patients, and many have been retrospective in design [8–13]. Furthermore, many patients have been lost during follow-up and the follow-up

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time has often been short. Hence, the remaining long-term risk to develop late complications needs to be better defined in patients with HCV-associated liver cirrhosis after SVR. This will have an impact on the need for HCC surveillance after SVR has been achieved.

The aim of this study was to prospectively evaluate the long-term effect of antiviral therapy on the risk of developing HCC, liver complications, and liver-related death in a cohort of 351 HCV patients with liver cirrhosis. To minimize the loss of patients during follow-up, complementary data from the national registries were used.

## PATIENTS AND METHODS

### Patients

Members of the Swedish Hepatitis Group were invited to participate in this multicenter study on HCV patients with liver cirrhosis designed to evaluate the risk of developing HCC, liver-related complications, and death. Patients with a diagnosis of HCV-associated liver cirrhosis, without known HCC at the time of diagnosis, were included in the Registry of Hepatitis C Cirrhosis. Patients with a diagnosis of HCC within 6 months after diagnosis of cirrhosis and those with a liver transplant were excluded. In total, 506 patients were consecutively included in the cohort during January 2001–July 2009 from 6 university hospitals in Sweden, with participating departments of gastroenterology and hepatology and infectious diseases at Karolinska University Hospital, Malmö University Hospital, Lund University Hospital, Sahlgrenska University Hospital, and Uppsala University Hospital.

Questionnaires at the time of diagnosis of cirrhosis and at follow-up were collected. The medical history, physical examination, biochemical tests, and virologic data were stored in a

central database at the Department of Gastroenterology and Hepatology, Karolinska University Hospital, Stockholm.

All patients were anti-HCV and HCV RNA positive. The cirrhosis diagnosis was based on liver biopsies from 1984 to 2009 ( $n = 364$  [72%]) or a clinical evaluation including biochemical parameters, clinical signs of portal hypertension, and/or radiologic findings consistent with cirrhosis. One hundred eighty-three (38%) patients were diagnosed with cirrhosis prior to 2001.

In total, 351 patients were selected from the Registry of Hepatitis C Cirrhosis for this study. The inclusion criteria were Child-Pugh class A cirrhosis without prior decompensation, defined as a history of ascites, variceal bleeding, and hepatic encephalopathy, at inclusion and no other concomitant liver diseases. Patients who lacked a Child-Pugh classification at the time of inclusion ( $n = 6$ ), had coinfection with hepatitis B ( $n = 6$ ) or human immunodeficiency virus ( $n = 5$ ), had hemochromatosis ( $n = 4$ ) or autoimmune hepatitis ( $n = 5$ ), or had a Child-Pugh classification of B ( $n = 81$ ) or C ( $n = 26$ ) were excluded, as were Child-Pugh class A patients who had a prior history of decompensation at inclusion ( $n = 22$ ). The baseline characteristics of the 351 compensated Child-Pugh class A included patients are shown in Table 1. The regional ethics committees in all participating centers approved the study.

### Treatment

In Sweden, combination therapy with peg-IFN and RBV was introduced in 2000–2001. Most of our patients treated during the follow-up period thus received peg-IFN alfa-2a or 2b plus RBV according to Swedish consensus [14]. One hundred twenty-three (35%) had previously received antiviral therapy, of whom 23 (7%) had achieved SVR before their inclusion in the study. Prior treatment experience could consist of only IFN

**Table 1. Baseline Demographics of Patients With Compensated Child-Pugh Class A Cirrhosis, Consisting of Patients With Sustained Virologic Response (SVR), Non-SVR, and Untreated**

Characteristic	All ( $n = 351$ )	SVR ( $n = 110$ )	Non-SVR ( $n = 193$ )	Untreated ( $n = 48$ )	P Value		
					SVR vs Non-SVR	Non-SVR vs Untreated	SVR vs Untreated
Male sex	242 (69%)	72 (65%)	135 (70%)	35 (73%)	.52	.73	.53
Age, y, mean $\pm$ SD	51 $\pm$ 9	50 $\pm$ 9	53 $\pm$ 8	58 $\pm$ 9	.11	<.0001*	<.0001*
RNA level, median log IU/mL (IQR)	5.9 (5.5–6.4)	5.9 (5.4–6.3)	6.0 (5.4–6.4)	5.9 (5.5–6.2)	.29	.26	.74
History of alcohol intake >50 g/d	71 (20%)	16 (15%)	42 (22%)	13 (27%)	.22	.44	<.0001*
Diabetes mellitus	69 (20%)	16 (15%)	40 (21%)	13 (27%)	.22	.34	.23
Genotype	$n = 316$	$n = 91$	$n = 183$	$n = 43$	<.0001*	.49	<.0001*
1	158 (50%)	22 (24%)	108 (59%)	28 (65%)			
Non-1	158 (50%)	69 (76%)	75 (41%)	15 (35%)			

Data are presented as No. (%) unless otherwise specified.

Abbreviations: IQR, interquartile range; SD, standard deviation; SVR, sustained virologic response.

\* Statistically significant ( $P < .05$ ).

injections 3 times per week ( $n = 35$ ), IFN in combination with RBV ( $n = 57$ ), or experience of both therapies ( $n = 31$ ).

SVR was defined as undetectable HCV RNA at end of treatment and follow-up 6 months after treatment end. The clinical routine was to also test HCV RNA at 12–18 months after end of therapy. No patient was HCV RNA positive at this time point.

Among 351 patients in this cohort, 110 (31%) patients achieved SVR, 193 (55%) were treated but failed to achieve SVR (“non-SVR”), and 48 patients remained untreated.

Quantitative and qualitative HCV RNA tests were performed with commercial assays, available at the respective hospital. At Karolinska University Hospital, HCV RNA was assessed with the Amplicor HCV test (Roche Diagnostics, Mannheim, Germany, sensitivity of 50 IU/mL) before 2000; with the Quantiplex HCV-RNA 2.0 test (Bayer Diagnostics, Emeryville, California, lower limit 0.2 mEq/mL) from 2000 to 2001; with the Quantiplex HCV RNA version 3.0 between 2001 and 2006; and with the Roche Amplicor/Cobas TaqMan test (detection limit 15 IU/mL) after 2006.

### Diagnosis of HCC, Follow-up, and Endpoints of the Study

The diagnosis of HCC was confirmed on the basis of a verified focal liver lesion by imaging techniques in accordance with the American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines [2, 15].

The 351 patients were followed up with the start date set as the date of cirrhosis diagnosis, or at the start of this cohort on 1 January 2001, whichever occurred latest. Follow-time at risk was divided into 3 categories: non-SVR, SVR, and untreated person-time. The patients contributed to follow-up time in untreated until the first treatment. Depending on the treatment response, the patients were then contributing to either follow-up time in non-SVR or SVR person-time instead. Because patients could receive >1 treatment during the follow-up period, patients could contribute to different time categories.

The occurrence of death, liver transplant, or the end of the study period (31 July 2009) was set as the endpoint. Liver transplant was considered to be a liver-related death. All endpoint data were obtained from the detailed questionnaires and patient journals and supplemented with information from the registries, described below.

Twenty-four (7%) patients were no longer being followed up at the participating hospital at the end of the follow-up period. For these patients, complementary data on HCC, hospitalizations due to liver-related causes, or death, were retrieved from registries concerning follow-up information. Three (0.8%) patients had moved abroad during the follow-up period and were censored at their last clinical visit.

### National Registries

All Swedish residents are assigned a 10-digit personal identification number that is used in all contacts with the healthcare

system. To obtain complete information concerning patients no longer being followed up at participating hospitals, we sent the personal identification numbers of our patients to the National Board of Health and Welfare and received data about cancer, date, and cause of death and diagnosis at the time of hospitalization from the Cancer, Causes of Death, and National Patient (Inpatient Registry) Registries, respectively.

Reporting all newly diagnosed malignant tumors to the Cancer Registry is mandatory for both clinicians and pathologists, and >95% of all detected tumors have been reported [16]. The Swedish Registry of Causes of Death contains information on virtually all deceased persons in the country ( $\geq 99.5\%$  since 1997), including the date and cause of death. The Swedish National Patient (Inpatient Registry) contains information about all residents who are hospitalized. The completeness of the registry since 1987 is estimated to be 98%–99%.

### Statistical Analyses

Continuous variables are presented as mean (SD) or median (range) and categorical variables as frequencies (percentages). Student  $t$  test and  $\chi^2$  test were used. The effect of age (50–59 vs <50 years or >60 vs <50 years), sex, alcohol consumption (<50 or >50 g/day), diabetes, and genotype (genotype 1 vs non-genotype 1) on incidence of HCC or any complication (HCC and liver complications) was tested by Cox regression.

The incidence of HCC, liver-related complications, and disease-free survival in relation to SVR status was estimated as the number of events occurring during non-SVR or untreated time, and SVR time divided by the corresponding person-time at risk in the groups. The effect of SVR was analyzed by Cox regression. The time scale used was calendar time since 1 January 2001 and SVR was considered as a time-dependent covariate. Models were also tested with adjustment for alcohol consumption, age, sex, and diabetes. Results are presented as hazard ratios (HRs) together with 95% confidence intervals, estimated using the profile likelihood method. Survival curves with respect to SVR status were estimated from the cumulative hazard functions for SVR, non-SVR, and untreated follow-up time obtained from the Cox regression models, and significant differences were assessed by testing  $HR = 1$  using Wald tests. The effects of SVR were also analyzed comparing the risks <3 years and >3 years after SVR. All tests were 2-sided and a  $P$  value of <.05 was considered statistically significant. Data analysis was performed with SAS 9.2 software (SAS Institute, Cary, North Carolina).

## RESULTS

A total of 351 patients with HCV-associated liver cirrhosis were enrolled and followed up for up to 8.6 years (mean, 5.3 [SD, 2.8] years), consisting of 110 patients with SVR and 193 patients with non-SVR and 48 untreated patients.

**Table 2. Incidence Rates of Hepatocellular Carcinoma, Liver Complication, Liver-Related Death, and All Death per 100 Person-Years for Sustained Virologic Response (SVR), Non-SVR, and Untreated Person-Time**

Endpoint	SVR					SVR vs Non-SVR					Non-SVR					Untreated					Untreated vs Non-SVR				
	Events, No.	PY	Rate	HR (95% CI)	P Value	Events, No.	PY	Rate	HR (95% CI)	P Value	Events, No.	PY	Rate	HR (95% CI)	P Value	Events, No.	PY	Rate	HR (95% CI)	P Value	Events, No.	PY	Rate	HR (95% CI)	P Value
HCC	6	589	1.0	0.38 (.14–.88)	.04*	26	1129	2.3			14	347	4.0	2.10 (1.05–4.01)	.03*										
Any decompensation	5	583	0.9	0.23 (.08–.53)	.002*	35	1092	3.2			16	326	4.9	1.92 (1.01–3.48)	.04*										
Ascites	4	583	0.7	0.23 (.07–.59)	.006*	28	1103	2.5			14	331	4.2	2.06 (1.03–3.93)	.03*										
Variceal bleeding	0	595	0.0	0.00 (.00–.44)	NA	8	1151	0.7			6	342	1.8	3.24 (1.04–9.60)	.03*										
Encephalopathy	1	594	0.2	0.28 (.01–1.74)	.24	5	1158	0.4			4	346	1.2	3.88 (.93–15.1)	.05										
Liver-related death	4	595	0.7	0.18 (.05–.45)	.001*	35	1162	3.0			16	352	4.5	2.01 (1.07–3.60)	.02*										
Overall death	11	595	1.8	0.36 (.18–.68)	.003*	48	1162	4.1			18	353	5.1	1.57 (.88–2.68)	.11										

HRs were calculated using hazard during non-SVR person-time as reference, and compared to hazards in SVR and untreated person-time. 95% CIs are shown. Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; NA, not applicable; PY, person-years; SVR, sustained virologic response. \*Statistically significant ( $P < .05$ ).

### Incidence of HCC

Six (5%) of the 110 patients with SVR developed HCC during follow-up (after mean 5.4 [SD, 2.6] years of follow-up), corresponding to an incidence of 1.0 per 100 person-years (PY; Table 2). HCC was diagnosed in 2 patients within 1 year after SVR (0.5 and 7.7 months), and the other 4 at 2.4, 7.4, 7.4, and 7.6 years after achieving SVR. HCV RNA was tested at the diagnosis of HCC in 4 of these patients, and they were all negative. None had varices at the time of SVR or developed any other liver complications during follow-up. Among the 6 patients with HCC who had achieved SVR, 5 were male, 3 had diabetes mellitus, and 1 had history of alcohol abuse. Two patients had genotype 1a and 2 had non-genotype 1 (genotype 2 or 3a); the genotype was missing in the remaining 2 patients. One patient underwent liver transplant due to his HCC.

The incidence rate for HCC was significantly higher in non-SVR and untreated person-time with 2.3 and 4.0 per 100 PY, respectively ( $P = .04$  and  $P = .03$ , respectively).

Only age and sex were found to be baseline factors significantly affecting the incidence of HCC (age 50–59 vs <50 years: HR, 2.45 [95% confidence interval {CI}, 1.16–5.61],  $P = .02$ ; age >60 vs <50 years: HR, 3.32 [95% CI, 1.48–7.90],  $P = .004$ ; male vs female: HR, 2.09 [95% CI, 1.06–4.62],  $P = .047$ ). For any complication (HCC and liver complication), none of the tested baseline factors were found to significantly affecting the outcome.

### Liver-Related Complications

In patients with SVR, 4 (3.6%) developed ascites, 1 (0.9%) hepatic encephalopathy, and none variceal bleeding during follow-up. Ascites was diagnosed 2, 13, 13, and 48 months after SVR had been achieved. None of these patients developed HCC, 3 were males, and none had excessive alcohol consumption or

had diabetes mellitus. Two, however, had esophageal varices at the time of inclusion. One patient developed liver encephalopathy 4.1 years after SVR had been achieved.

The risk of developing any liver-related complication was significantly lower in SVR than non-SVR person-time ( $P = .002$ ) and highest in untreated person-time ( $P = .04$ ).

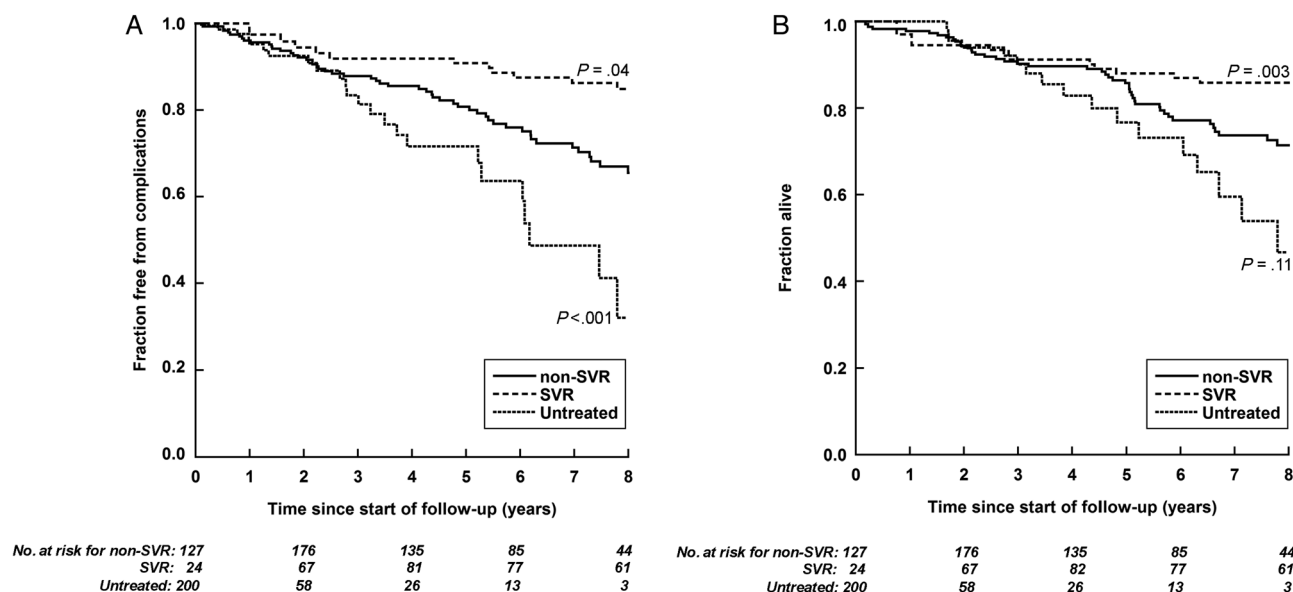
The Figure 1 shows the cumulative risk of any complication (HCC and any liver complication). The incidence rate for SVR, non-SVR, and untreated person-time was 1.9, 5.1, and 7.5 per 100 PY, respectively. The risk for any liver complication was significantly lower in SVR person-time and higher in untreated person-time, compared to the risk in non-SVR person-time ( $P < .0001$  and  $P = .04$ , respectively).

### Liver-Related and Overall Deaths

Eleven (10%) patients with SVR died during follow-up, 4 (3.6%) of liver-related causes with HCC. The causes of death for the other 7 patients were lung cancer ( $n = 1$ ), pulmonary embolism ( $n = 1$ ), pneumonia ( $n = 1$ ), pancreatitis ( $n = 1$ ), pancreatic cancer ( $n = 2$ ) and, in 1, unknown. One (0.9%) patient underwent liver transplant due to HCC. Fifty-two (22%) of 241 patients lacking SVR (non-SVR and untreated) died of liver-related causes and 15 (6%) patients of other causes. Liver transplant was performed in 23 patients (10%).

The incidence rate for liver-related death was 0.7 per 100 PY in SVR patients (Table 2), which was significantly lower compared to non-SVR (3.0 per 100 PY;  $P = .001$ ) or untreated (4.5 per 100 PY;  $P = .02$ ) patients.

Significantly lower incidence rate for overall death was seen in SVR with 1.9 per 100 PY, compared to 4.1 per 100 PY in non-SVR person-time ( $P = .003$ ). Thirty-six percent of overall deaths were due to liver-related causes in patients with SVR,



**Figure 1.** Kaplan-Meier curves depicting the relationship between absence of clinical events in sustained virologic response (SVR), non-SVR, and untreated follow-up time. Cox regression was used with non-SVR person-time as reference = 1, and compared to SVR and untreated time. *P* values of these analyses are shown in the graph. The number of patients at risk in each group are shown for 0, 2, 4, 6, and 8 years of follow-up time. *A*, Follow-up time versus fraction free from hepatocellular carcinoma and any liver-related complication. *B*, Follow-up time versus fraction free from overall death. Abbreviation: SVR, sustained virologic response.

whereas the majority of overall deaths (78%) consisted of liver-related causes in patients with non-SVR.

The risks for HCC, any complication, liver-related death, overall death, or any of the mentioned events were analyzed <3 years and compared to those occurring >3 years after SVR had been achieved. The cutoff time point of 3 years was chosen due to the fact that this time point made the distribution of any events similar in the 2 time periods. None of the events were significantly reduced after 3 years of SVR. A trend was noted for a decreased risk of any event, but was not statistically significant (*P* = .05).

The difference of risk between SVR and non-SVR/untreated person-time in outcomes remained similar when adjusted for alcohol consumption, age, sex, and diabetes mellitus (data not shown).

## DISCUSSION

In this study, a total of 351 HCV-infected patients with compensated Child-Pugh class A liver cirrhosis were followed during long-term. This made it possible to evaluate the impact that SVR had on the risk to develop HCC, liver-related complications, and death. This prospectively followed cohort is to our knowledge the largest of cirrhotic HCV-infected patients with or without SVR so far studied. We found that SVR reduced the incidence of these outcomes but that the risk to develop HCC

remained during prolonged time after SVR had been achieved, but on a lower level. This highlights the fact that surveillance for HCC needs to be continued during long-term, also in patients who achieve SVR. This is further strengthened by the fact that all patients who died from liver-related causes after having achieved SVR had developed HCC. On the other hand, surveillance with ultrasound is thought to be costly for society and time consuming for the individual. The duration needed for long-term surveillance for HCC after SVR requires further studies.

SVR in cirrhotic patients has generally been 10%–15% lower than in noncirrhotic patients in the pivotal clinical trials and even lower in an everyday clinical setting [17]. Pivotal treatment studies with peg-IFN in combination with RBV have often included patients with advanced fibrosis (F3) and analyzed them together with cirrhotic patients (F4). The risk of liver complications and HCC may differ in these 2 groups, and cirrhotic patients more often fail to achieve SVR than F3 patients [18]. Previous studies on the impact of SVR have often suffered from a retrospective design, included relatively few cirrhotic patients with SVR and suffered from short follow-up periods and/or significant loss of patients during follow-up [8–10, 12, 13]. The effect that SVR has on HCC has therefore yielded diverging results on the reduction of the risk of developing HCC [4–8, 15]. Two studies have shown no significant reduction to develop HCC after SVR [7, 8]. In one prospective study, including both



F3 and F4 patients with a mean follow-up time of 3.5 years, the HCC incidence was significantly higher in patients lacking SVR (5.9/100 PY) than in patients with SVR (1.2/100 PY) [12]. We found that the risk of HCC was 1.0 per 100 PY in SVR patients. The risk for HCC was higher in untreated compared to non-SVR time, indicating a beneficial effect despite lack of SVR.

The time point when a new HCC was detected was within 1 year after SVR in 2 of 6 patients, possibly implicating that the cancer was already present but undetected before SVR was reached. In 3 patients, the HCC was detected late, 7 years after SVR. Hence, the risk of developing HCC can persist long-term after SVR. When analyzing the risk for HCC over time after SVR, the risk for HCC was numerically lower >3 years after SVR compared to <3 years after SVR was achieved. This difference, however, was not statistically significant. The lack of significance could have been caused by the low number of events after achievement of SVR, rendering this analysis a low statistical power.

A significantly lower incidence of liver-related complications and liver-related deaths after SVR has been noted in several studies [8–10, 12, 18–21], similar to our study. In meta-analyses with pooled data from both Asian and Western European studies, a reduced risk of HCC, liver-related morbidity, and mortality has been seen in patients with SVR [22, 23]. The risk for overall death was also significantly reduced in patients with SVR in our study, with the majority of deaths non–liver related.

In our study, no patient who achieved SVR developed variceal bleeding. This is in accordance with a prospective study including 34 cirrhotic patients with SVR followed over 12 years, in which none developed de novo esophageal varices during follow-up [11]. Endoscopic surveillance in cirrhotic patients who have achieved SVR is probably not necessary.

A common problem in follow-up studies is the frequent loss of patients during follow-up [12, 18]. In the present study, dropouts were very few (0.8%). This was achieved by using the Swedish registries to clarify the outcome in patients lost from the routine follow-up.

In this study, we do not have sequential measurement of liver fibrosis after achievement of SVR. The importance of fibrosis regression with vanishing cirrhosis seen in the HCV-related cirrhosis after SVR noted in earlier studies could thus not be assessed in our study [24], and the correlation between remaining fibrosis and long-term risk for HCC could not be analyzed.

To conclude, we found a reduced but persistent long-term risk of developing HCC after achievement of SVR in patients with HCV-related cirrhosis. This risk persisted at least 8 years after SVR had been achieved in some patients. This indicates that continued surveillance for HCC should be maintained during prolonged time periods.

## Notes

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**Potential conflicts of interest.** S. A. has given lectures with honoraria from Roche, MSD, Janssen, and Gilead. O. W. has been a consultant and given lectures with honoraria from MSD, Roche, Gilead, Janssen, Novartis, and BMS. H. V. has been given lectures with honoraria from MSD and received meeting expenses from Janssen and Roche. P. S. has been a consultant to Bayer Healthcare. A. E. has given lectures with honoraria from MSD and AstraZeneca. F. G. has given expert consultancy to Amgene. R. H. has received a research grant from Bayer Healthcare and given lectures with honoraria from MSD. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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