Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis

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Context Chronic hepatitis C virus (HCV) infection outcomes include liver failure, hepatocellular carcinoma (HCC), and liver-related death.

Objective To assess the association between sustained virological response (SVR) and all-cause mortality in patients with chronic HCV infection and advanced hepatic fibrosis.

Design, Setting, and Patients An international, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada of 530 patients with chronic HCV infection who started an interferon-based treatment regimen between 1990 and 2003, following histological proof of advanced hepatic fibrosis or cirrhosis (Ishak score 4-6). Complete follow-up ranged between January 2010 and October 2011.

Main Outcome Measures All-cause mortality. Secondary outcomes were liver failure, HCC, and liver-related mortality or liver transplantation.

Results The 530 study patients were followed up for a median (interquartile range [IQR]) of 8.4 (6.4-11.4) years. The baseline median (IQR) age was 48 (42-56) years and 369 patients (70%) were men. The Ishak fibrosis score was 4 in 143 patients (27%), 5 in 101 patients (19%), and 6 in 286 patients (54%). There were 192 patients (36%) who achieved SVR; 13 patients with SVR and 100 without SVR died (10-year cumulative all-cause mortality rate, 8.9% [95% CI, 3.3%-14.5%] with SVR and 26.0% [95% CI, 20.2%-28.4%] without SVR; $P<.001$). In time-dependent multivariate Cox regression analysis, SVR was associated with reduced risk of all-cause mortality (hazard ratio [HR], 0.26; 95% CI, 0.14-0.49; $P<.001$) and reduced risk of liver-related mortality or transplantation (HR, 0.06; 95% CI, 0.02-0.19; $P<.001$), the latter occurring in 3 patients with SVR and 103 without SVR. The 10-year cumulative incidence rate of liver-related mortality or transplantation was 1.9% (95% CI, 0.0%-4.1%) with SVR and 27.4% (95% CI, 22.0%-32.8%) without SVR ($P<.001$). There were 7 patients with SVR and 76 without SVR who developed HCC (10-year cumulative incidence rate, 5.1%; 95% CI, 1.3%-8.9%; vs 21.8%; 95% CI, 16.6%-27.0%; $P<.001$), and 4 patients with SVR and 111 without SVR experienced liver failure (10-year cumulative incidence rate, 2.1%; 95% CI, 0.0%-4.5%; vs 29.9%; 95% CI, 24.3%-35.5%; $P<.001$).

Conclusion Among patients with chronic HCV infection and advanced hepatic fibrosis, sustained virological response to interferon-based treatment was associated with lower all-cause mortality.

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CHRONIC HEPATITIS C VIRUS (HCV) infection is a major cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease. The incidence of HCV-related cirrhosis and its complications is expected to increase in upcoming years.[1,2] Davis et al[2] estimated that currently 25% of the approximately 3.5 million US patients with chronic HCV infection have cirrhosis and that the proportion of patients with cirrhosis is likely to increase up to 45% by 2030.

Pegylated interferon and ribavirin treatment is effective in 50% to 80% of patients.[3-5] Sustained virological response (SVR) is defined as absence of viremia 24 weeks after cessation of all antiviral medication.[6] Although SVR has long-term durability, data on the relationship with improved survival to support its use as a surrogate end point of

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antiviral therapy is scarce.[7] Demonstrating direct clinical benefits would better justify the use of intensive and costly antiviral therapy, such as expensive direct antiviral agents, which improve treatment efficacy when added to pegylated interferon and ribavirin for many patients with chronic HCV genotype 1 infection.[8-10]

Our group previously demonstrated that SVR is associated with a reduced occurrence of liver failure and liver-related deaths in patients with chronic hepatitis C (CHC) and advanced hepatic fibrosis.[11] Studies in other western populations confirmed these findings.[12-14] Whether these beneficial effects of SVR also result in a reduced all-cause mortality in the high-risk population of patients with chronic HCV infection and severe hepatic fibrosis is currently not clear.

Because all-cause mortality is the most definite clinical end point with clear interpretation, knowledge about the effect of treatment on all-cause mortality is important in considering antiviral treatment. The Centers for Disease Control and Prevention recently recommended birth-cohort screening for HCV infection[15]; thus, scientific proof that SVR to interferon-based treatment is associated with lower all-cause mortality is also important for screening purposes.

With this large, international, multicenter, long-term follow-up study, we investigated whether achievement of SVR vs without SVR is associated with a prolonged overall survival in 530 patients with CHC and advanced hepatic fibrosis.

METHODS

Patients

All patients included in our international, multicenter cohort from 5 large hepatology units of tertiary care centers in Europe and Canada were reevaluated by reviewing the medical charts.[11] This cohort included all consecutive patients with CHC who started interferon-based treatment between 1990 and 2003 if they had histological proof of advanced fibrosis or cirrhosis (Ishak score 4-6). Histologically, Ishak fibrosis score 4 is characterized by fibrous expansion of most portal areas with marked portal-to-portal as well as portal-to-central bridging; Ishak fibrosis score 5, by marked portal-to-portal and/or portal-to-central bridging with occasional nodules (early cirrhosis); and Ishak fibrosis score 6, by probable or definite cirrhosis.[16] The interobserver agreement concerning the degree of fibrosis is strong, especially regarding the presence or absence of cirrhosis.[17] Interferon-based therapy has been standard of practice since the beneficial effects of recombinant interferon alpha in patients with chronic HCV infection were described.[18,19] Patients coinfected with human immunodeficiency virus or hepatitis B virus and patients with a history of liver failure were excluded.

Compared with the 479 patients analyzed in our prior report, we extended this cohort with 51 additional patients who were eligible to be included in the analyses according to the same inclusion and exclusion criteria.[11] In contrast with the prior data collection, these patients now either had their medical chart available for data acquisition or had follow-up beyond 24 weeks after the end of treatment with a documented virological response.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was reviewed and approved by the ethics committee in the center of the primary investigators, which was the Erasmus Medical Center in Rotterdam, the Netherlands. Ethical approval in the participating centers was obtained according to the local regulations. According to the standards of the local ethics committees, written informed consent was obtained from patients visiting the outpatient clinics, and written or oral informed consent was obtained from patients contacted by telephone. If patients were not reached, the general practitioner of the patients was contacted by their treating physician without informed consent. The ethics committee approved the above-described procedure as our study was considered a low-risk study using anonymized patient data.

Data were obtained on patient demographics (sex, age, height, and weight), severity of fibrosis (Ishak fibrosis score), antiviral treatment (type of medication, treatment period, virological response, previous treatment), and presence of diabetes mellitus or a history of severe alcohol use as stated in the chart by the treating physician. In the participating centers, the use of more than 50 g/d of alcohol was considered severe alcohol use. Virology data (HCV genotype, anti-hepatitis B core antigen) and baseline laboratory data (platelet count, bilirubin, albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT]) within 6 months before treatment were also registered. Liver biopsy samples were scored by local experienced pathologists who were unaware of virological or long-term clinical outcome after treatment.

Complete follow-up was defined as death or clinical follow-up beyond January 1, 2010, which was approximately half a year before the start of data collection. For patients without ongoing clinical follow-up to 2010, the patient or primary care physician was recontacted. Patients were invited for a single visit to obtain a detailed history and perform a physical examination, laboratory testing, and ultrasonographic evaluation. If the patient was unable to visit, the patient or primary care physician were asked to answer a structured questionnaire over the telephone. If the patient and primary care physician could not be reached, the patient was censored at the last available follow-up visit.

Clinical Outcome Measures

The primary outcome measure of the study was all-cause mortality. Secondary clinical outcome measures were liver failure, HCC, and liver-related mortality or liver transplantation. Liver transplantation events and liver-related mortality were analyzed as a

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combined end point. The cause of death was determined by the treating physician. Death caused by liver failure, primary liver malignancy, or variceal bleeding was considered liver related. Death due to extrahepatic malignancy, cardiovascular or cerebrovascular events, or other causes was considered not liver related.

The definition of liver failure included an episode of either ascites confirmed by ultrasonography, bleeding varices, jaundice with a bilirubin level of more than 2.05 mg/dL (to convert to μmol/L, multiply by 17.104), or overt hepatic encephalopathy. The diagnosis of HCC was based on histopathological confirmation or 2 coincident imaging techniques (computer tomography, magnetic resonance imaging, or contrast-enhanced ultrasonography), showing a focal lesion of more than 2 cm with arterial-phase hyperenhancement or 1 imaging technique showing a focal lesion of more than 2 cm with arterial-phase hyperenhancement in the presence of an α-fetoprotein level of more than 400 ng/mL.[20]

Statistical Analyses

At the initial design of the study in 2004, the power calculation indicated that 137 patients with SVR would be needed to show a quantitative survival benefit of 8.8% after 5 years with a power of 90%, and a level of significance of .05, assuming a 5-year mortality of 2.5% in patients with SVR based on mortality data from the general population and a 5-year mortality of 11.3% in patients without SVR based on a model assessing the natural history of chronic HCV infection.[21,22]

The baseline characteristics were compared between patients with and without SVR after the baseline treatment, using the Mann-Whitney test for continuous variables and the χ^2 test for categorical variables.

The association between SVR and all-cause mortality, liver-related mortality or liver transplantation, HCC, and liver failure was estimated with the Cox proportional hazards regression method. Twenty-four weeks after end of treatment was defined as time 0, because patients with undetectable HCV RNA at this time point were classified as having attained SVR, and others were classified as without SVR. Patients were not censored for any reason other than loss to follow-up for the all-cause mortality analyses. Deceased patients were censored at the time of death for the nonmortality outcomes. Patients experiencing liver failure were thus not censored in the analyses for HCC, or vice versa. Treated patients who were lost to follow-up or experienced a clinical event before 24 weeks after end of treatment were, per definition, not able to attain SVR status before dropout or reaching the event. For this reason, these patients were not included in the analyses. Because retreatment in patients without SVR could result in SVR, patients without SVR were able to switch from a non-SVR to a SVR status during the follow-up. To correct for patients who changed their response status, SVR was included as a time-dependent covariate in the Cox proportional hazards regression analyses. Other baseline variables that were considered included age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), genotype 1 vs no genotype 1, genotype 3 vs no genotype 3, Ishak fibrosis score, treatment naive vs treatment experienced, treatment duration, presence of diabetes, history of severe alcohol use, anti-hepatitis B core antigen positivity, platelet count, AST/ALT ratio, and the albumin and bilirubin level. Age, sex, SVR, and variables with $P<.20$ in univariate analyses were included in multivariate analyses. All multivariate analyses were adjusted for the year treatment started, and stratified by treatment center, to control for possible heterogeneity between centers. Akaike's Information Criteria was used to compare the goodness of fit between models. The proportionality assumption was checked graphically via the log-minus-log plots for categorical variables and by including an interaction term between the variable and log-transformed follow-up time for both continuous and categorical variables. Interactions between SVR and other baseline variables included in the final model were explored.

Survival curves for the SVR status were constructed by using a clock-reset approach. Patients who switched from the non-SVR to the SVR group were censored in the non-SVR group at the time of SVR. The time of SVR was then reset as time zero for the patients' further follow-up in the SVR group. The difference between the survival curves in the non-SVR and SVR groups was assessed with univariate Cox proportional hazards regression analyses with SVR as a time-dependent covariate.

Sensitivity analyses using multiple imputation to impute missing values were performed.[23,24]

All statistical tests were 2-sided, and $P<.05$ was considered statistically significant. The significance level for interactions was set at .01 to correct for multiple testing. SPSS version 17.0.2 (SPSS Inc) was used for all statistical analyses.

RESULTS

Study Population

In total, 546 patients with CHC and advanced hepatic fibrosis started an interferon-based regimen at the participating centers between 1990 and 2003. Despite our attempts to recontact all patients, 8 patients were lost to follow-up before reaching 24 weeks after end of treatment. Six of these 8 patients were HCV RNA positive. For the other 2 patients, HCV RNA was not documented, but both had an elevated ALT level at the last visit. These patients were excluded from the analyses. Three patients were diagnosed with HCC and 5 patients developed liver failure within 24 weeks after end of treatment, who were thus also excluded from the analyses. All these patients had showed virological nonresponse or relapse; therefore, the total study cohort consisted of 530 patients.

Overall, 192 patients (36%) achieved SVR and 338 patients (64%) did not. Of these, 125 patients (65%) achieved

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SVR after the baseline treatment and were thus considered sustained responders for the entire study period. A total of 204 patients (60%) with initial non-SVR were retreated and 67 (33%) of them achieved SVR after a median (interquartile range [IQR]) of 5.8 (3.1-8.5) years of follow-up. The patients with successful retreatment were considered as patients without SVR in the analysis until after successful retreatment, at which point they were treated as patients with SVR for the remainder of follow-up.

The baseline treatment consisted of interferon monotherapy (approved by the US Food and Drug Administration [FDA] in 1991) in 175 patients (33%), interferon and ribavirin (FDA approval in 1998) in 148 patients (28%), and pegylated interferon and ribavirin (FDA approval of pegylated interferon in 2001) in 176 patients (33%). A minority of patients were treated with pegylated interferon monotherapy (3% [n=14]) or consensus interferon (FDA approval in 1997) with or without ribavirin (3% [n=17]).

TABLE 1 shows the baseline characteristics according to the initial virological response. The overall median (IQR) age was 48 (42-56) years and the majority of patients were men (70% [n=369]). The Ishak fibrosis score was 4 in 143 patients (27%), 5 in 101 patients (19%), and 6 in 286 patients (54%) and did not differ significantly between response groups (P=.41). As expected, patients without SVR were more often treated with non–pegylated interferon regimens and more frequently infected with HCV genotype 1.

Follow-up Duration

The median (IQR) follow-up duration was 8.4 (6.4-11.4) years. The last follow-up encounter among patients who survived and had complete follow-up ranged between January 2010 and October 2011. Follow-up was shorter for patients with SVR (median, 6.6 years; IQR, 5.0-8.3) than for patients without SVR (median, 8.1 years; IQR, 5.7-11.1; $P<.001$) because SVR occurred

Table 1. Baseline Characteristics According to Treatment Response[a]

Characteristics	Overall (N = 530)	With SVR (n = 125)	Without SVR (n = 405)	*P* Value[b]
Age, median (IQR), y	48 (42-56)	47 (43-54)	48 (42-56)	.57
Men	369/530 (70)	94/530 (75)	275/530 (68)	.12
BMI, median (IQR) (n = 401)	26.1 (23.6-29.3)	25.4 (23.1-28.5)	26.5 (24.0-29.5)	.06
Fibrosis score				
Ishak 4	143/530 (27)	38/125 (30)	105/405 (26)	.41
Ishak 5	101/530 (19)	26/125 (21)	75/405 (19)	
Ishak 6	286/530 (54)	61/125 (49)	225/405 (56)	
Hepatitis C virus genotype				
1	340/502 (68)	50/118 (42)	290/384 (76)	<.001
2	48/502 (10)	27/118 (23)	21/384 (5)	
3	88/502 (18)	36/118 (31)	52/384 (14)	
4	22/502 (4)	4/118 (3)	18/384 (5)	
Other	4/502 (1)	1/118 (1)	3/384 (1)	
Type of treatment				
Interferon monotherapy	175/530 (33)	9/125 (7)	166/405 (41)	<.001
Interferon and ribavirin	148/530 (28)	35/125 (28)	113/405 (28)	
Pegylated interferon monotherapy	14/530 (3)	4/125 (3)	10/405 (2)	
Pegylated interferon and ribavirin	176/530 (33)	75/125 (60)	101/405 (25)	
Consensus interferon (±ribavirin)	17/530 (3)	2/125 (2)	15/405 (4)	
Treatment duration, median (IQR), wk	26.3 (21.5-48.0)	47.7 (24.4-50.4)	24.3 (17.1-47.3)	<.001
Laboratory data, median (IQR)				
Platelet count, $\times 10^9$/L (n = 457)	151 (114-200)	164 (133-207)	145 (109-195)	.009
Albumin, g/L (n = 423)	42 (39-44)	43 (40-45)	42 (39-44)	.12
Bilirubin, mg/dL (n = 442)	0.76 (0.58-0.99)	0.64 (0.53-0.88)	0.82 (0.60-1.11)	<.001
AST/ALT ratio (n = 431)	0.70 (0.57-0.90)	0.67 (0.54-0.82)	0.71 (0.58-0.91)	.04
Treatment naive	477/530 (90)	112/125 (90)	365/405 (90)	.87
Year treatment started, median (IQR)	1999 (1996-2002)	2002 (1999-2002)	1998 (1995-2001)	<.001
Diabetes mellitus	66/530 (12)	11/125 (9)	55/405 (14)	.16
History of severe alcohol use	119/494 (24)	31/120 (26)	88/374 (24)	.61
Anti-HBc positivity	195/416 (47)	42/91 (46)	153/325 (47)	.88

Abbreviations: ALT, alanine aminotransferase; anti-HBc, anti-hepatitis B core antigen; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range; SVR, sustained virological response.
SI conversion: To convert bilirubin to μmol/L, multiply by 17.104.
[a] Data are presented as No./Total No. (%), unless otherwise noted. See "Methods" section for definitions of Ishak fibrosis scores.
[b] Baseline characteristics were compared between patients with and without SVR using the Mann-Whitney test for continuous variables and the χ^2 test for categorical variables.

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Table 2. Clinical Events According to Treatment Response

Outcomes	With SVR			Without SVR			*P* Value[b]
	Events, No.	Observation Period, Person-Years	Rate per 100 Person-Years (95% CI)	Events, No.	Observation Period, Person-Years	Rate per 100 Person-Years (95% CI)	
Any event[a]	18	1260	1.43 (0.77-2.09)	169	2921	5.79 (4.91-6.66)	<.001
All-cause mortality	13	1283	1.01 (0.46-1.56)	100	3410	2.93 (2.36-3.51)	<.001
Liver-related mortality or liver transplantation	3	1283	0.23 (<0.01-0.50)	103	3120	3.20 (2.58-3.82)	<.001
Hepatocellular carcinoma	7	1270	0.55 (0.14-0.96)	76	3222	2.63 (1.83-2.89)	<.001
Liver failure	4	1271	0.31 (<0.01-0.62)	111	3066	3.62 (2.95-4.29)	<.001

Abbreviation: SVR, sustained virological response.
[a] Any event is the composite of all analyzed outcomes, to which only the first event contributed in case of multiple events in an individual patient.
[b] *P* value is based on unadjusted Cox proportional hazards regression analyses, including SVR as a time-dependent covariate.

more often near the end of the inclusion period due to introduction of more effective combination treatment with pegylated interferon and ribavirin. In total, 454 patients (86%) had complete follow-up. Complete follow-up percentage did not differ significantly between response groups (84% in SVR group and 86% in without SVR group, $P=.53$). During the entire study period, 18 patients (9%) with SVR and 169 patients (50%) without SVR experienced at least 1 clinical outcome event (TABLE 2).

All-Cause Mortality

Thirteen patients (7%) with SVR and 100 patients (30%) without SVR died after prolonged follow-up of our cohort, which was more than 4 times the number of deaths registered during the first data collection (n=2 among patients with SVR and n=24 among patients without SVR).[11] There was a significant difference in the cumulative 10-year mortality rate between patients with SVR (8.9%; 95% CI, 3.3%-14.5%) and without SVR (26.0%; 95% CI, 20.2%-28.4%; $P<.001$) (FIGURE). Cox proportional hazards regression analysis showed that SVR was associated with a statistically significant reduction in the hazard of overall death (adjusted hazard ratio [HR], 0.26; 95% CI, 0.14-0.49; $P<.001$) (TABLE 3, model 1).

Other baseline factors significantly associated with all-cause mortality in multivariate analysis were older age, HCV genotype 3 infection, higher Ishak fibrosis score, presence of diabetes, and a history of severe alcohol use. Patients with HCV genotype 3 infection were younger (median [IQR] age, 44 [40-49] years) compared with patients without genotype 3 infection (median [IQR], 49 [43-57] years; $P<.001$), and after correction for age, the relationship with genotype 3 became apparent. Among 311 patients for whom HCV genotype and a probable transmission route was known, patients with HCV genotype 3 infection were more frequently infected through injection drug use (41 of 63 patients [65%] with genotype 3 infection vs 106 of 248 patients [43%] without genotype 3 infection, $P=.002$). The HR of HCV genotype 3 infection remained similar (HR, 2.35; 95% CI, 1.11-4.95; $P=.03$) when corrected for injection drug use as route of transmission, which showed a higher but not statistically significant risk for all-cause mortality itself (HR, 1.51; 95% CI, 0.71-3.21; $P=.28$).

The laboratory markers of liver disease severity were included in a second model. These laboratory markers were all available in a representative subgroup of 390 patients (74%) (Table 3, model 2). The estimated HR of SVR for all-cause mortality was essentially the same (HR, 0.25; 95% CI, 0.12-0.53; $P<.001$) in this analysis. Corrected for SVR, the all-cause mortality risk did not differ for patients with all 4 laboratory markers available compared with the patients who were missing at least 1 laboratory marker (HR, 0.89; 95% CI, 0.57-1.37; $P=.59$). Furthermore, also after multiple imputation for missing values, performed as sensitivity analyses, the HR of SVR for all-cause mortality remained statistically significant (adjusted HR, 0.28; 95% CI, 0.15-0.52; $P<.001$).

Subgroup analyses showed that the association between SVR and reduced all-cause mortality remained in patients with a history of severe alcohol use (adjusted HR, 0.04; 95% CI, 0.00-0.40; $P=.006$), in patients with most severe cirrhosis (adjusted HR, 0.22; 95% CI, 0.10-0.48; $P<.001$), as well as in patients older than 55 years (adjusted HR, 0.28; 95% CI, 0.11-0.71; $P=.008$). However, the interactions between SVR and these covariates were not statistically significant.

Liver-Related Mortality or Liver Transplantation

Of the 100 deaths in patients without SVR, the cause was liver-related in 70 patients (70%), not liver-related in 15 patients (15%), and unknown in another 15 patients (15%). A liver-related, not liver-related, or unknown cause of death was present in 3 patients (23%), 6 patients (46%), and 4 patients (31%) with SVR, respectively. Among the total 21 non–liver-related mortalities, 8 patients died of extra-hepatic malignancy, 4 of a cerebrovascular or cardiovascular event, 2 because of advanced pulmonary disease, and 7 of other not liver-related causes. None of the patients with SVR underwent liver transplantation in

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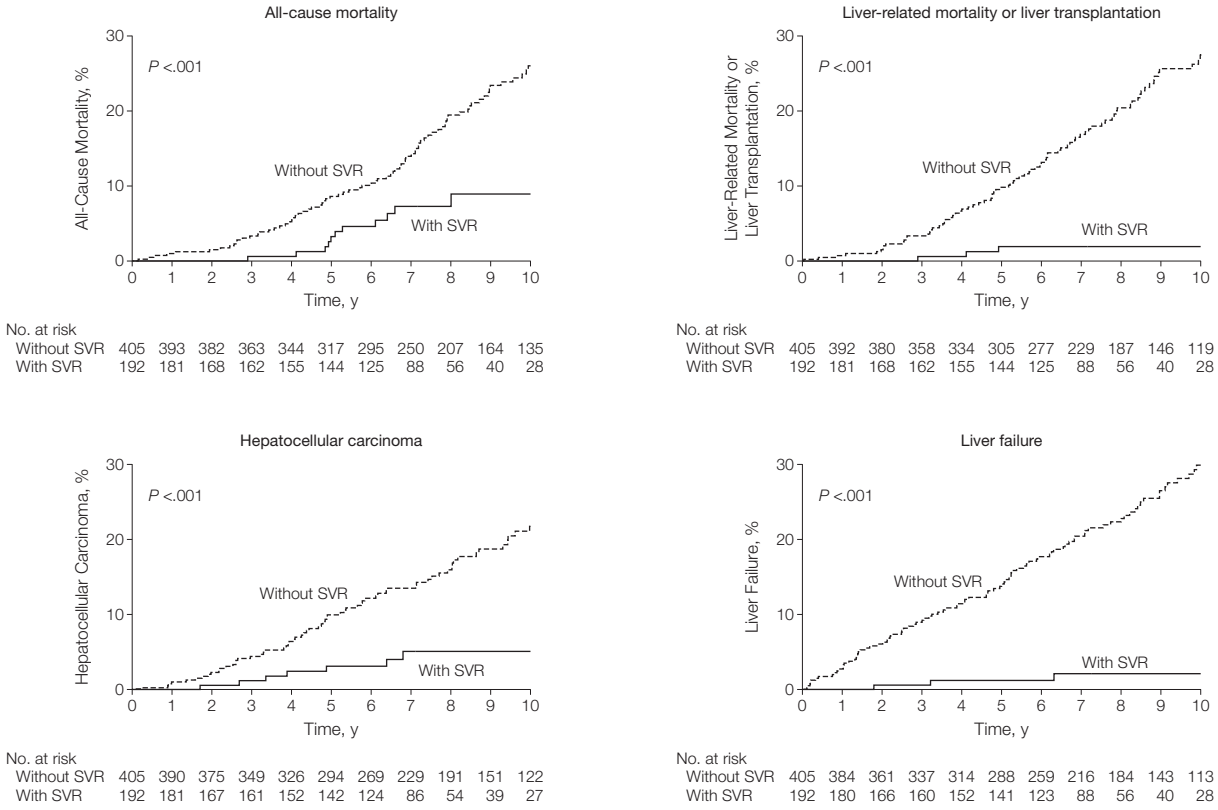
contrast with 46 patients without SVR, of whom 13 died during follow-up. Liver-related mortality or liver transplantation occurred in 103 patients (30%) without SVR and in only 3 patients (2%) with SVR (Table 2).

In comparison, after the previous data collection, we found that liver-related mortality or liver transplantation occurred in 34 patients without SVR and only 1 patient with SVR.[11] The 10-year cumulative incidence risk of liver-related mortality or liver transplantation was 1.9% (95% CI, 0.0%-4.1%) in patients with SVR and 27.4% (95% CI, 22.0%-32.8%) in patients without SVR ($P<.001$) (Figure). This resulted in a lower hazard in patients achieving SVR (adjusted HR, 0.06; 95% CI, 0.02-0.19; $P<.001$) (Table 4). In contrast with the overall mortality model, diabetes (HR, 0.86; 95% CI, 0.45-1.66; $P=.66$) and HCV genotype 3 infection (HR, 1.18; 95% CI, 0.62-2.27; $P=.62$) were not associated with liver-related mortality or liver transplantation. Having Ishak fibrosis score 5 or 6 was a risk factor (HR, 4.02; 95% CI, 1.67-9.69; $P=.002$ and HR, 4.84; 95% CI, 2.16-10.85, respectively; $P<.001$). Further adjusting for laboratory markers of liver disease severity showed that the HR of SVR for liver-related mortality or liver transplantation remained statistically significant (adjusted HR, 0.05; 95% CI, 0.01-0.22; $P<.001$).

Liver-Related Morbidity

Seven patients with SVR (4%) were diagnosed with HCC, up to 6.8 years after SVR was achieved. In the without SVR group, HCC occurred in 76 patients (22%). One hundred fifteen patients, of whom only 4 had SVR, had liver failure with or without signs of portal hypertension (Table 2). Ascites was the most frequent first sign of liver failure occurring in 75 cases (65%), followed by 23 cases with variceal bleed-

Figure. Survival Outcomes for All-Cause Mortality, Liver-Related Mortality or Liver Transplantation, Hepatocellular Carcinoma, and Liver Failure in Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis With and Without Sustained Virological Response (SVR)



Survival curves for each outcome were constructed using a clock-reset approach; patients who switched from the without SVR to the with SVR group due to successful retreatment during follow-up were censored in the without SVR group at the time of SVR. The time of SVR was then defined as time zero for their further follow-up in the SVR group. Statistical significance between the survival curves in the without and with SVR groups was assessed with univariate Cox proportional hazards regression analyses, including SVR as a time-dependent covariate. The 10-year cumulative occurrence rates for all-cause mortality were 8.9% (95% CI, 3.3%-14.5%) for with SVR and 26.0% (95% CI, 20.2%-28.4%) for without SVR; for liver-related mortality or liver transplantation, 1.9% (95% CI, 0.0%-4.1%) for with SVR and 27.4% (95% CI, 22.0%-32.8%) for without SVR; for hepatocellular carcinoma, 5.1% (95% CI, 1.3%-8.9%) for with SVR and 21.8% (95% CI, 16.6%-27.0%) for without SVR; and for liver failure, 2.1% (95% CI, 0.0%-4.5%) for with SVR and 29.9% (95% CI, 24.3%-35.5%) for without SVR.

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ing (20%), 11 with hepatic encephalopathy (10%), and 6 with jaundice only (5%). One patient reached SVR due to retreatment after the ascites had resolved. Three of 4 patients with SVR and liver failure had ascites and 1 patient was jaundiced.

After 10 years, the cumulative occurrence of HCC was 5.1% (95% CI, 1.3%-8.9%) in patients with SVR and 21.8% (95% CI, 16.6%-27.0%) in patients without SVR ($P<.001$) (Figure). The 10-year cumulative liver failure rate was 2.1% (95% CI, 0.0%-4.5%) in patients with SVR vs 29.9% (95% CI, 24.3%-35.5%) in patients without SVR ($P<.001$) (Figure). The risk of HCC (adjusted HR, 0.19; 95% CI, 0.08-0.44; $P<.001$) and the risk of liver failure (adjusted HR, 0.07; 95% CI, 0.03-0.20; $P<.001$) were reduced in patients with SVR (Table 4). More severe hepatic fibrosis, older age, and a history of severe alcohol use were risk factors for both HCC and liver failure. Male sex, presence of diabetes at baseline, and HCV genotype 3 infection were significantly associated with HCC occurrence only (Table 4). The adjusted HR of SVR was 0.17 (95% CI, 0.06-0.47; $P=.001$) for HCC and 0.06 (95% CI, 0.02-0.21; $P<.001$) for liver failure, when adding laboratory markers of liver disease to the multivariate Cox proportional hazards regression models.

COMMENT

In our international, multicenter, long-term follow-up study, SVR was associated with prolonged overall survival. The risk of all-cause mortality was almost 4-fold lower in patients with SVR compared with patients without SVR. Our study with a long follow-up duration demonstrated a lower risk for all-cause mortality in patients with chronic HCV infection and advanced hepatic fibrosis who achieved SVR. In addition, we were able to further establish and quantify the risk reduction of HCC, liver failure, and liver-related mortality or liver transplantation in patients with SVR.

Although prior studies have described a clinical benefit of SVR in patients with CHC and severe hepatic fibrosis, most did not investigate all-cause mortality as a single outcome. A reduced liver-related mortality has been

Table 3. Cox Proportional Hazards Regression Analyses for All-Cause Mortality[a]

	All-Cause Mortality							
	Model 1 (n = 493)				Model 2 (n = 368)[b]			
	No. of Events	No. of Patients	HR (95% CI)	*P* Value	No. of events	No. of patients	HR (95% CI)	*P* Value
Virological response								
Without SVR	92	315	1 [Reference]		60	224	1 [Reference]	
With SVR[c]	13	178	0.26 (0.14-0.49)	<.001	9	144	0.25 (0.12-0.53)	<.001
Age, per y			1.09 (1.06-1.12)	<.001			1.08 (1.05-1.11)	<.001
Sex								
Female	30	147	1 [Reference]		18	102	1 [Reference]	
Male	75	346	1.52 (0.93-2.48)	.09	51	266	1.35 (0.69-2.67)	.38
HCV genotype								
Non–genotype 3	87	410	1 [Reference]		55	303	1 [Reference]	
Genotype 3	18	83	2.08 (1.18-3.66)	.01	14	65	2.68 (1.37-5.25)	.004
Diabetes mellitus								
No	84	432	1 [Reference]		52	318	1 [Reference]	
Yes	21	61	1.76 (1.02-3.01)	.04	17	50	2.46 (1.28-4.72)	.007
History of severe alcohol use								
No	76	380	1 [Reference]		48	276	1 [Reference]	
Yes	29	113	2.20 (1.32-3.67)	.002	21	92	2.38 (1.21-4.68)	.01
Fibrosis score				.09				.67
Ishak 4	14	134	1 [Reference]		6	93	1 [Reference]	
Ishak 5	14	96	1.29 (0.60-2.77)	.52	10	73	1.65 (0.56-4.91)	.37
Ishak 6	77	263	1.87 (1.02-3.45)	.04	53	202	1.38 (0.54-3.50)	.50
Platelet count, per 10×10^9/L			NA	NA			0.90 (0.85-0.96)	.002
Bilirubin, per mg/dL			NA	NA			1.01 (0.95-1.07)	.83
Albumin, per g/L			NA	NA			0.99 (0.92-1.07)	.80
AST/ALT ratio, per 0.1			NA	NA			1.11 (1.02-1.22)	.02

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; HR, hazard ratio; NA, not available; SVR, sustained virological response.
[a] Multivariate Cox proportional hazards regression analyses to adjust the HR of SVR for all-cause mortality. Both models were adjusted for the year treatment started and stratified by treatment center to control for possible heterogeneity between centers.
[b] A complete case analysis was performed after inclusion of the laboratory markers of liver disease severity. In 26% of the patients, either baseline platelet count, bilirubin, albumin, or AST/ALT ratio was missing.
[c] Included as a time-dependent variable to control for patients who changed their response status from without SVR to with SVR due to successful retreatment during the follow-up.

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demonstrated, but this remains a suboptimal surrogate end point.[12-14] A reduction in liver-related death may not directly translate into an overall survival benefit, as liver-related mortality in patients without SVR could mask an overall deteriorating clinical condition leading to death due to indirect causes related to cirrhosis, such as increased risk of infections in patients with cirrhosis or increased risk of vehicle accidents in patients with low-grade encephalopathy. Our finding of reduced all-cause mortality should be free of this bias.

In another partially prospective study, the association of SVR with all-cause death and liver transplantation as a combined end point was analyzed.[14] The adjusted cumulative proportion of patients who died or underwent liver transplantation after 7.5 years of follow-up was higher in patients not responding to pegylated interferon and ribavirin therapy (27.2%) compared with patients with virological breakthrough or relapse (4.4%) or SVR (2.2%).

In a Spanish cohort of patients with cirrhosis, the 5-year mortality was 2% in patients with SVR vs 14% in patients without SVR.[25] Multivariate analysis for all-cause mortality was not reported, probably because of the limited number of deaths in the relatively short follow-up of 2.9 years. In a large and predominantly male population of US veterans followed up for a median of 3.8 years, 5-year mortality rates of 6.7% to 8.0% in patients with SVR vs rates of 14.4% to 24.4% in patients without SVR were reported.[26] Because only 9% to 16% of the included patients were registered as having cirrhosis, the relatively high death rate in the study of the US veterans may be due to other comorbidities in this patient population. Both of these studies included patients treated with pegylated interferon and ribavirin combination treatment from 2001 onwards, but we included all consecutive patients with CHC with histological-proven advanced fibrosis from the first interferon treatment available. We performed time-dependent Cox proportional hazards regression analyses in which the virological response status could change from non-SVR to SVR during the follow-up, as is the case in the real-life setting.

A further new finding of our study was the approximately 2-fold increased risk of all-cause mortality and HCC in patients with HCV genotype 3 infection compared with patients without genotype 3 infection. Genotype 3 infection has been associated with more rapid fibrosis progression.[27] The association with genotype 3 infection remained after correction for fibrosis stage and laboratory markers of liver disease severity. A higher risk of HCC in patients with genotype 3 infection has been found previously and could be explained by hepatic steatosis.[28] Steatosis is more frequently observed in patients with HCV genotype 3 infection and is a risk factor

Table 4. Cox Proportional Hazards Regression Analyses for Secondary Clinical Outcomes[a]

	Liver-Related Mortality or Liver Transplantation (n = 483)				Hepatocellular Carcinoma (n = 491)				Liver Failure (n = 498)			
	No. of Events	No. of Patients	HR (95% CI)	*P* Value	No. of Events	No. of Patients	HR (95% CI)	*P* Value	No. of Events	No. of Patients	HR (95% CI)	*P* Value
Virological response												
Without SVR	96	309	1 [Reference]		68	312	1 [Reference]		102	317	1 [Reference]	
With SVR[b]	3	174	0.06 (0.02-0.19)	<.001	7	179	0.19 (0.08-0.44)	<.001	4	181	0.07 (0.03-0.20)	<.001
Age, per y			1.04 (1.01-1.06)	.005			1.09 (1.06-1.12)	<.001			1.05 (1.02-1.07)	<.001
Sex												
Female	22	143	1 [Reference]		14	145	1 [Reference]		29	149	1 [Reference]	
Male	77	340	1.50 (0.90-2.52)	.12	61	346	2.00 (1.07-3.76)	.03	77	349	1.11 (0.70-1.75)	.67
HCV genotype												
Non–genotype 3	86	402	1 [Reference]		62	407	1 [Reference]		95	413	1 [Reference]	
Genotype 3	13	81	1.18 (0.62-2.27)	.62	13	84	2.07 (1.06-4.05)	.03	11	85	0.78 (0.39-1.57)	.49
Diabetes mellitus												
No	87	425	1 [Reference]		61	431	1 [Reference]		92	437	1 [Reference]	
Yes	12	58	0.86 (0.45-1.66)	.66	14	60	2.01 (1.07-3.80)	.03	14	61	1.14 (0.62-2.06)	.68
History of severe alcohol use												
No	73	373	1 [Reference]		54	379	1 [Reference]		72	385	1 [Reference]	
Yes	26	110	1.71 (1.02-2.88)	.04	21	112	2.20 (1.23-3.94)	.008	34	113	2.57 (1.61-4.10)	<.001
Fibrosis score				.001				.04				<.001
Ishak 4	8	131	1 [Reference]		8	134	1 [Reference]		7	134	1 [Reference]	
Ishak 5	21	93	4.02 (1.67-9.69)	.002	17	97	2.93 (1.23-6.95)	.02	23	98	5.64 (2.35-13.51)	<.001
Ishak 6	70	259	4.84 (2.16-10.85)	<.001	50	260	2.62 (1.20-5.70)	.02	76	266	6.30 (2.82-14.11)	<.001

Abbreviations: HCV, hepatitis C virus; HR, hazard ratio; SVR, sustained virological response.
[a] Multivariate Cox proportional hazards regression models to adjust the HR of SVR. Both models were adjusted for the year treatment started and stratified by treatment center to control for possible heterogeneity between centers.
[b] Included as a time-dependent variable to control for patients who changed their response status from without SVR to with SVR due to successful retreatment during the follow-up.

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for HCC, independent of cirrhosis.[29,30] Recognition of worse clinical outcome in patients with HCV genotype 3 infection should encourage clinicians to treat this population now rather than to await newer antiviral agents.

The development from interferon monotherapy to pegylated interferon and ribavirin combination therapy has led to an improvement of SVR rates. Accordingly, patients without SVR in our study were more frequently treated with interferon monotherapy and thus earlier during the inclusion period compared with patients with SVR. Duration of treatment was shorter in patients without SVR, both because treatment efficacy is reduced if discontinued early because of intolerability to interferon and because of recommended on-treatment stopping rules for nonresponse.[6] Because more advanced liver disease is associated with virological nonresponse, it was expected that the SVR group had a higher platelet count, lower bilirubin level, lower AST/ALT ratio, and lower prevalence of Ishak fibrosis score 6. Nevertheless, our extensive multivariate analyses including all the markers of liver disease severity showed that SVR was independently associated with reduced all-cause mortality and liver-related mortality as well as liver-related morbidity. There remains, however, the possibility of unmeasured confounding.

There are several limitations with our study. Due to improvements of antiviral treatment, it is inevitable that the follow-up duration was shorter in patients with SVR than in patients without SVR. It is unlikely, however, that this follow-up difference had a substantial effect on our results because the clinical events followed linear patterns over time. Furthermore, cohort studies can be susceptible to bias when many patients are lost to follow-up and this is associated with the end points that are studied. It was therefore important that we recontacted patients and achieved a very high complete follow-up percentage of 86%. Data on laboratory markers at baseline was expected to be missing at random and indeed availability of laboratory markers was not associated with mortality. Furthermore, after using multiple imputation to impute missing values, the HR of SVR for all-cause mortality remained essentially the same. The retrospective nature of our study could have led to a selection of a relatively healthy cirrhotic HCV population, because patients with most severe clinical characteristics are usually not considered for antiviral treatment. Because of the long follow-up duration and high number of patients with severe cirrhosis (Ishak fibrosis score 6), we registered sufficient events to show a clear decrease in all-cause mortality and liver-related morbidity in patients with SVR.

In conclusion, our study indicates that SVR was associated with improved overall survival in patients with chronic HCV infection and advanced hepatic fibrosis.

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