# Sustained Virologic Response and Clinical Outcomes in Patients with Chronic Hepatitis C and Advanced Fibrosis

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**Background:** Clinical outcomes of chronic hepatitis C infection in patients with advanced fibrosis include liver failure, hepatocellular carcinoma, and death.

**Objective:** To investigate whether sustained virologic response to treatment for hepatitis C is associated with improved clinical outcomes.

**Design:** Retrospective cohort study.

**Setting:** 5 hepatology units of tertiary care centers in Europe and Canada caring for patients with chronic hepatitis C treated between 1990 and 2003.

**Patients:** Consecutively treated patients with chronic hepatitis C who had biopsy-proven advanced fibrosis or cirrhosis (Ishak score, 4 to 6).

**Measurements:** Sustained virologic response, defined as absence of detectable hepatitis C virus RNA at 24 weeks after the end of treatment, and clinical outcomes, defined as death (liver-related or non–liver-related), liver failure, and hepatocellular carcinoma.

**Results:** Of 479 patients, 29.6% had sustained virologic response and 70.3% did not. Median follow-up was 2.1 years (interquartile range, 0.8 to 4.9 years). Four patients with and 83 without sustained virologic response had at least 1 outcome event. Sustained virologic response was associated with a statistically significant reduction in the hazard of events (adjusted hazard ratio, 0.21 [95% CI, 0.07 to 0.58]; $P = 0.003$). The effect was largely attributable to a reduction in liver failure, which developed in no patients with and 42 patients without sustained virologic response (5-year occurrence, 0% vs. 13.3% [CI, 8.4% to 18.2%]; unadjusted hazard ratio, 0.03 [CI, 0.00 to 0.91]).

**Limitations:** Because few events occurred in the sustained virologic response group, the study had limited ability to detect differences between groups in individual outcomes. In addition, the study was retrospective; selection and survival biases may therefore influence estimates of effect.

**Conclusion:** Sustained virologic response to treatment is associated with improved clinical outcomes, mainly prevention of liver failure, in patients with chronic hepatitis C and advanced fibrosis.

More than 170 million people are chronically infected with the hepatitis C virus (HCV) (1). Patients with chronic hepatitis C may develop decompensated liver disease and hepatocellular carcinoma (HCC). This risk is highest in patients with advanced fibrosis.

The effectiveness of treatment for chronic hepatitis C is usually evaluated by the number of patients who reach sustained virologic response, which is a surrogate marker. Several large studies have suggested that successful treatment with pegylated interferon and ribavirin may halt and even reverse hepatic fibrosis. Cammà and colleagues (2) found that sustained virologic response was associated with a reduction in fibrosis in 1013 patients with chronic hepatitis C who had had pre- and posttreatment liver biopsies and had received interferon or pegylated interferon. Among 3010 patients for whom pre- and posttreatment biopsy results were available in Poynard and associates' study (3), reversal of fibrosis occurred in 12% of those treated for 24 weeks with standard interferon and up to 24% of those treated with an optimal schedule of pegylated interferon and ribavirin. Although Poynard and associates observed regression of cirrhosis in 49% of their patients after successful treatment, a clinical benefit of pegylated interferon treatment has not yet been demonstrated for patients who have already developed advanced fibrosis or cirrhosis.

Until now, reports of the long-term benefit of standard interferon therapy for patients with cirrhosis have been disappointing, because few patients achieved sustained virologic response (4). Large studies from Japan indicate that persons treated before cirrhosis develops experience the maximum benefit of sustained virologic response (5). Because sustained virologic response rates after therapy with pegylated interferon plus ribavirin are higher than those after interferon monotherapy, studies are needed to evaluate the effect of the former therapy on solid clinical end points, such as liver failure, HCC, and survival, and to establish whether sustained virologic response leads to an improved long-term outcome in this high-risk population. We therefore sought to investigate whether sustained virologic response, compared with nonresponse, leads to an

### Context

Most studies of hepatitis C treatment report effects on surrogate measures, such as liver enzymes and viral load.

### Contribution

The authors compared clinical outcomes in patients with chronic hepatitis C and advanced fibrosis who did and did not have sustained virologic response to treatment. They found that sustained virologic response decreased patients' hazard of liver failure.

### Caution

Sustained virologic response also seemed to be associated with a reduction in liver cancer and liver-related death, but not enough events occurred in the sustained virologic response group to detect differences between groups in these other outcomes.

### Implication

Sustained virologic response to chronic hepatitis C treatment is associated with a reduction in clinical events, mainly liver failure.

—The Editors

improved clinical outcome for patients with chronic hepatitis C and advanced fibrosis.

## METHODS

We enrolled all consecutive patients with chronic hepatitis C who had biopsy-proven advanced fibrosis or cirrhosis (Ishak score, 4 to 6) that was treated with an interferon-based regimen between 1990 and 2003 at 5 large hepatology units of tertiary care centers in Europe and Canada. Patients were excluded if they were co-infected with hepatitis B virus or HIV. Patients with decompensated liver disease were not eligible for treatment and were therefore not included in the study.

Approval was obtained from the ethics committees of each participating study site. Local investigators identified all eligible patients, and the principal investigator then visited each center to enter the individual patient data from the chart into a central database in a standardized and predefined manner.

We obtained data on patient sex and age and details of the treatment (duration, interferon vs. pegylated interferon, ribavirin, and treatment-naive vs. previous nonresponse). Age was determined at the start of the last treatment. Virologic data (genotype, baseline viral load, anti–hepatitis B core antigen positivity), biochemical data (bilirubin, albumin), and hematologic data (platelet count, prothrombin time/quick time) were measured in the certified laboratories of participating hospitals and were corrected centrally for local normal values. Local pathologists, who all had extensive experience in scoring samples from patients with viral hepatitis, scored liver biopsy samples. To assess HCV RNA status, all participating centers used commercial polymerase chain reaction tests from Roche Diagnostics (Basel, Switzerland) with a detection limit of 100 to 500 IU/mL. Before these tests became commercially available in 1994, they used nested in-house polymerase chain reaction tests, in which plasma HCV RNA was analyzed in duplicate by polymerase chain reaction using 2 sets of primers derived from the 5′ noncoding region followed by a hybridization assay; this method is described elsewhere for the different centers (6–9). These sensitive HCV RNA tests were also used to define the absence of detectable HCV RNA at 24 weeks after the end of treatment. Patients who did not respond or who had relapse with detectable virus at this time were classified as nonresponders.

### Clinical Events

The primary outcomes of the study were the composite of death (liver-related and non–liver-related), liver failure, and HCC and each outcome individually. Patients who had more than 1 event contributed only 1 (the first that occurred) to analyses of the association between sustained virologic response and "any event." Liver transplantation counted as liver-related death at the time of transplantation, but patients who survived the procedure were regarded as alive in the analysis of overall death.

Liver failure was defined as ascites confirmed by ultrasonography or computed tomography, bleeding esophageal varices, jaundice with a bilirubin level greater than 35 $\mu$mol/L, or hepatic encephalopathy. Hepatocellular carcinoma was confirmed by cytohistologic examination or was diagnosed if 2 coincident imaging techniques (ultrasonography, computed tomography, or magnetic resonance imaging) showed a focal lesion larger than 2 cm with arterial hypervascularization, or if 1 imaging technique showed a focal lesion larger than 2 cm with arterial hypervascularization in the presence of an $\alpha$-fetoprotein level greater than 400 ng/mL. For HCC, the date of the event was when the diagnosis was confirmed histologically or radiographically. If follow-up was incomplete, the treating physician contacted the patient. If the patient could not be reached, the treating physician contacted the patient's general practitioner to complete the follow-up.

### Statistical Analysis

Baseline clinical characteristics were compared by using Mann–Whitney $U$ and chi-square tests. Logistic regression was used to analyze which of the following baseline factors were associated with response to interferon-based treatment: age; sex; previous nonresponse; treatment duration; treatment including ribavirin; treatment with pegylated interferon versus standard interferon; fibrosis stage; genotype; pretreatment bilirubin level, platelet count, and albumin level; viral load; treatment period (1990 to 1997 or 1998 to 2005); and treatment center. The **Appendix** (available at www.annals.org) shows our covariate and model selection strategy and regression diagnostics.

Twenty-four weeks after the end of treatment was used

as time 0 for classifying patients as responders or non-responders, because the definition of sustained virologic response is undetectable serum HCV RNA by sensitive molecular tests at that time. The Kaplan–Meier method was used to estimate the effect of sustained virologic response on clinical events, and groups were compared by using log-likelihood tests.

Separate Cox proportional hazards models were developed to determine which baseline factors were associated with development of any clinical event, overall death, liver-related and non–liver-related death, liver failure, and HCC. The final models included sustained virologic response, age, sex, previous nonresponse, bilirubin level, albumin level, platelet count, and treatment center as covariates and were stratified by treatment period (1990 to 1997 or 1998 to 2005) to represent evolution in the evaluation and treatment of hepatitis C since 1990 (and especially since the introduction of ribavirin in 1998). The reported hazard ratios for bilirubin level, albumin level, and platelet count are the relative increases in hazard associated with increases of 10 $\mu$mol/L for bilirubin level, 10 g/L for albumin level, and $10 \times 10^9$ cells/L for platelet count. Anti–hepatitis B core antigen positivity was a risk factor for HCC, but the hazard of HCC associated with anti–hepatitis B core antigen positivity was not proportional over time; we therefore stratified the analysis of risk for HCC by serum anti–hepatitis B core antigen positivity.

Because baseline bilirubin level, albumin level, or platelet count was missing in 28.5% of patients, we used multiple imputation to impute missing values (10, 11); the Markov chain Monte Carlo method with a single chain (PROC MI in SAS software [SAS Institute, Cary, North Carolina]) was applied to construct 10 complete data sets. All baseline factors, time-related factors, and events related to the analyses were entered into the imputation procedure and, if necessary, transformed to conform to the multivariate normality assumption. Cox analysis (PROC PHREG) or logistic regression analysis (PROC LOGISTIC) was then run on each data set, and the results and inference were combined by using PROC MIANALYZE. All statistical analyses were performed by using SAS software, version 9.1.3.

### Role of the Funding Source

The Netherlands Organisation for Health Research and Development had no influence on the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

## RESULTS

### Sample

Five hundred forty-one patients with advanced fibrosis were treated with an interferon-based regimen at the par-

**Table 1.** Patient Characteristics at the Start of the Last Treatment*

| Characteristic | Overall (n = 479) | Patients with Sustained Virologic Response (n = 142) | Patients without Sustained Virologic Response (n = 337) | P Value |
|---|---|---|---|---|
| Age, y | 48 (43–56) | 48 (42–56) | 49 (43–56) | 0.45 |
| Men, n (%) | 332 (69) | 104 (73) | 228 (68) | 0.23 |
| Genotype 1, n (%)† | 280 (59) | 56 (39) | 224 (67) | <0.001 |
| Anti–hepatitis B core antigen positivity, n (%) | 141 (30) | 38 (27) | 103 (31) | 0.46 |
| Treatment, n (%) | | | | <0.001 |
| Interferon | 131 (27) | 14 (10) | 117 (35) | |
| Interferon plus ribavirin | 130 (27) | 41 (29) | 89 (26) | |
| Pegylated interferon | 10 (2.1) | 4 (2.8) | 6 (1.8) | |
| Pegylated interferon plus ribavirin | 208 (43) | 83 (59) | 125 (37) | |
| Previous nonresponse, n (%) | 143 (30) | 35 (25) | 108 (32) | 0.106 |
| Duration of treatment, wk | 26 (21–48) | 47 (25–52) | 24 (16–47) | <0.001 |
| Treatment period, n (%) | | | | <0.001 |
| 1990–1997 | 134 (28) | 16 (11) | 118 (35) | |
| 1998–2005 | 345 (72) | 126 (89) | 219 (65) | |
| Follow-up, y | 2.1 (0.8–4.9) | 1.1 (0.3–2.9) | 2.8 (1.2–5.9) | <0.001 |
| Viral load, $\times 10^5$ IU/mL‡ | 8.1 (4.0–25) | 8.5 (2.7–39) | 8.0 (4.4–23) | 0.75 |
| Bilirubin level, $\mu$mol/L | 9.8 (7.3–12.0) | 9.2 (7.3–12.4) | 10.2 (7.5–14.0) | 0.016 |
| Albumin level, g/L | 41 (38–43) | 41 (38–44) | 41 (38–43) | 0.161 |
| Platelet count, $\times 10^9$ cells/L | 160 (116–207) | 166 (129–210) | 151 (110–204) | 0.073 |
| Fibrosis, n (%) | | | | 0.45 |
| Ishak score 4 | 120 (25) | 41 (29) | 79 (23) | |
| Ishak score 5 | 94 (20) | 27 (19) | 67 (20) | |
| Ishak score 6 | 265 (55) | 74 (52) | 191 (57) | |

* Data are expressed as median (interquartile range), unless otherwise noted.
† Genotype was missing in 12% of patients.
‡ Viral load was measured by local hybridization or polymerase chain reaction assays and could be retrieved in 68% of patients.

ticipating centers. We excluded 52 patients because they had not reached 24 weeks after the end of treatment and 10 patients because they developed a clinical event within 24 weeks of follow-up after their last treatment.

The study cohort thus consists of 479 patients, of whom 142 (30%) had sustained virologic response and 337 (70%) did not. Seventy-two percent of the patients had complete follow-up until 1 January 2005, 6 months before data acquisition.

One hundred thirty-one patients (27%) received interferon monotherapy, 130 (27%) received interferon and ribavirin, 10 (2.1%) received pegylated interferon monotherapy, and 208 (43%) received pegylated interferon and ribavirin (**Table 1**). One hundred forty-three patients (30%) had no response to a previous course of interferon-based treatment; of these, 73 (51%) received 2 treatment courses and 70 (49%) received 3 treatment courses. The median interval between 2 treatment courses was 4.2 years (interquartile range, 1.8 to 6.4 years). Overall, the median treatment duration was 26 weeks (interquartile range, 21 to 48 weeks). Fifty-one patients received less than 12 weeks of treatment, yet 2 had sustained virologic response. The median treatment duration was 24 weeks for nonresponders and 47 weeks for patients with sustained virologic response (**Table 1**). Among nonresponders, genotype 1 was predominant.

The following factors were associated with sustained virologic response in multivariable analysis: non–type 1 genotype (odds ratio, 2.65 [95% CI, 1.79 to 3.92]), treatment-naive versus previous nonresponse (odds ratio, 1.31 [CI, 1.01 to 1.71]), treatment including ribavirin (odds ratio, 1.96 [CI, 1.38 to 2.79]), and treatment duration of more than 35 weeks versus less than 20 weeks (odds ratio, 3.83 [CI, 2.63 to 5.58]). The associations with pegylated interferon versus standard interferon (odds ratio, 1.14 [CI, 0.87 to 1.49]), pretreatment serum bilirubin levels (odds ratio, 0.63 [CI, 0.39 to 1.02]), platelet count (odds ratio, 0.98 [CI, 0.94 to 1.03]), and albumin levels (odds ratio, 1.31 [CI, 0.62 to 2.77]) were not statistically significant. There was no statistically significant effect of treatment center on sustained virologic response ($P = 0.102$). Overall follow-up was shorter for patients with sustained virologic response than for those without response, because patients who were treated after the introduction of ribavirin in 1998 had higher response rates. Twelve percent (16 of 134) of the patients treated before 1998 achieved sustained virologic response, compared with 37% (126 of 345) of patients treated during or after 1998 (**Table 1**). We performed an analysis on the subgroup of patients treated from 1998, when ribavirin was introduced. Of these 345 patients, 122 of 126 (97%) with sustained virologic response and 213 of 219 (97%) without response received ribavirin. The median follow-up was 0.9 year (interquartile range, 0.2 to 2.3 years) for patients with sustained virologic response and 1.6 years (interquartile range, 0.7 to 3.2 years) for those without response.

### Any Event

Four patients with sustained virologic response and 83 nonresponders had at least 1 event. The difference in the proportion of patients experiencing events at 5 years statistically significantly differed between groups (**Figure**), and sustained virologic response was associated with a significant reduction in the hazard of events (adjusted hazard ratio, 0.21 [CI, 0.07 to 0.58]; $P = 0.003$) (**Table 2**). The **Appendix Table** (available at www.annals.org) shows estimates of associations between other variables and clinical outcomes. In a subgroup analysis of patients treated since ribavirin was introduced in 1998, the difference in occurrence of any clinical events remained significant (hazard ratio, 0.20 [CI, 0.05 to 0.86]; $P = 0.031$).

### Overall Death and Non–Liver-Related Death

The **Appendix Figure** (available at www.annals.org) shows the relationship between overall, liver-related, and non–liver-related death and transplantation. Two patients with and 24 patients without sustained virologic response died during follow-up. One patient with and 5 patients without sustained virologic response died of non–liver-related causes. The overall and non–liver-related mortality rates at 5 years did not differ between patients with and those without sustained virologic response (**Figure**), and sustained virologic response was associated with a non–statistically significant reduction in the hazard of death (adjusted hazard ratio, 0.31 [CI, 0.07 to 1.38]; $P = 0.124$) (**Table 2**).

### Liver-Related Death and Transplantation

The **Appendix Figure** (available at www.annals.org) shows the relationship between overall, liver-related, and non–liver-related death and transplantation. One patient with and 16 without sustained virologic response died of a liver-related cause, and 18 patients without response underwent orthotopic liver transplantation. Liver-related death at 5 years differed significantly between patients with and those without sustained virologic response (**Figure**), and sustained virologic response was associated with a non–statistically significant reduction in the hazard of liver-related death (adjusted hazard ratio, 0.19 [CI, 0.02 to 1.44]; $P = 0.107$) (**Table 2**).

### Liver Failure

No patient with sustained virologic response developed signs of liver failure during follow-up. Forty-two patients developed liver failure. The incidence of liver failure was statistically significantly decreased among patients with sustained virologic response compared with those without response at 5 years (**Figure**). In an unadjusted analysis, sustained virologic response was associated with a statistically significant reduction in the hazard of liver failure (unadjusted hazard ratio, 0.03 [CI, 0.00 to 0.91]) (**Table 2**). The adjusted hazard of liver failure with sustained virologic response could not be quantified because no patient with sustained virologic response developed liver failure during follow-up.

*Figure.* **Kaplan–Meier curves showing the occurrence (95% CI) of clinical events in patients with and without sustained virologic response (SVR).**
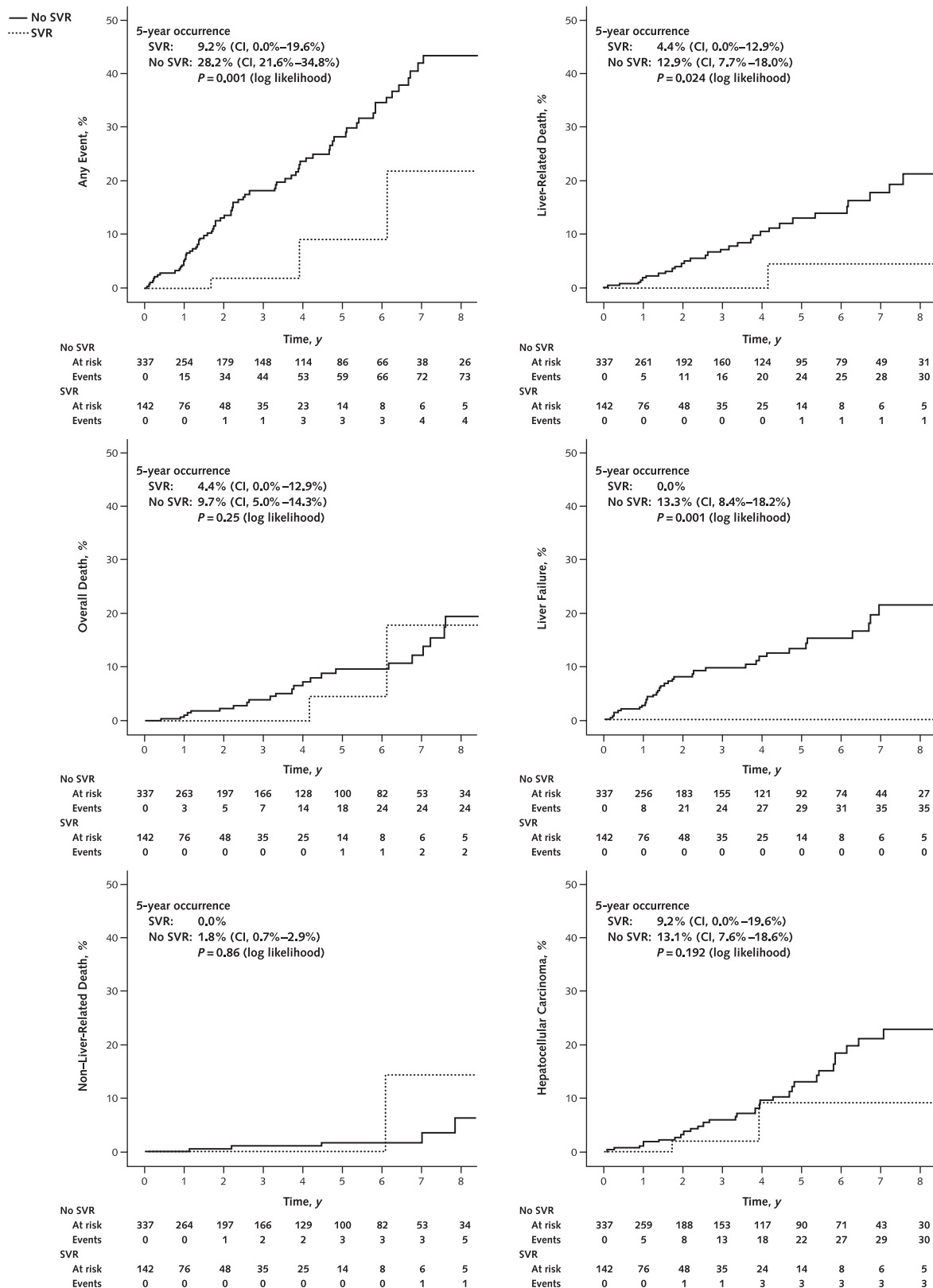
**Table 2.** Clinical Outcomes, by Response to Treatment

| Outcome | Patients with Sustained Virologic Response | | | Patients without Sustained Virologic Response | | | Hazard Ratio (95% CI) | | P Value* |
|---|---|---|---|---|---|---|---|---|---|
| | Events, n | Observation Period, patient-years | Events per 10 000 Patient-Years (95% CI), n | Events, n | Observation Period, patient-years | Events per 10 000 Patient-Years (95% CI), n | Unadjusted | Adjusted† | |
| Any event | 4 | 280 | 143 (2–283) | 83 | 1107 | 750 (594–905) | 0.20 (0.07–0.55) | 0.20 (0.07–0.58) | 0.003 |
| Overall death | 2 | 281 | 71 (0–170) | 24 | 1243 | 193 (116–270) | 0.44 (0.10–1.87) | 0.31 (0.07–1.38) | 0.124 |
| Liver-related death‡ | 1 | 281 | 36 (0–106) | 34 | 1200 | 283 (189–377) | 0.14 (0.02–1.03) | 0.19 (0.02–1.44) | 0.107 |
| Non–liver-related death§ | 1 | 281 | 36 (0–106) | 5 | 1245 | 40 (5–75) | 1.21 (0.14–10.6) | – | – |
| Liver failure‖ | 0 | 281 | 0 (0–2) | 42 | 1150 | 365 (257–474) | 0.03 (0.00–0.91) | – | – |
| Hepatocellular carcinoma | 3 | 280 | 107 (0–228) | 32 | 1157 | 277 (182–371) | 0.46 (0.14–1.52) | 0.46 (0.12–1.70) | 0.25 |

* For adjusted hazard ratios.
† Analyses are adjusted for age, sex, previous nonresponse, bilirubin level, albumin level, platelet count, treatment center, and treatment period (1990–1997 or 1998–2005). The analysis of risk for hepatocellular carcinoma was also adjusted for anti–hepatitis B core antigen positivity.
‡ Includes 17 deaths (1 patient with and 16 without sustained virologic response) and 18 patients who had liver transplantation (all of whom did not have sustained virologic response). Patients with liver transplantations are included in "Liver-related death" but not in "Overall death," unless a patient died after liver transplantation (as occurred in 3 patients without response). See also the **Appendix Figure**, available at www.annals.org.
§ Too few non–liver-related deaths occurred to assess the effect of sustained virologic response on non–liver-related death in multivariable analysis.
‖ The effect of sustained virologic response on liver failure could not be quantified in multivariable analysis, because no patient with sustained virologic response developed liver failure during follow-up.

### Hepatocellular Carcinoma

Three patients with and 32 patients without sustained virologic response developed HCC. Twenty-two of these patients (63%) had a histologic diagnosis. In all but 1 patient, HCC was confirmed in the explant after transplantation; this patient had received ethanol injection of the tumor before transplantation. The incidence of HCC at 5 years did not differ between patients with sustained virologic response and nonresponders (**Figure**), and sustained virologic response was associated with a non–statistically significant reduction in the hazard of HCC (adjusted hazard ratio, 0.46 [CI, 0.12 to 1.70]; $P = 0.25$) (**Table 2**).

The hazard of HCC in patients with anti–hepatitis B core antigen positivity was not proportional and decreased over time (hazard ratio, 4.21 [CI, 1.25 to 14.2] in the first 2.5 years and 1.61 [CI, 0.68 to 3.80] after 2.5 years).

The 3 patients with sustained virologic response and HCC were still negative for serum HCV RNA at the time of HCC diagnosis. Baseline radiologic imaging was available for these patients and did not show any signs of HCC. Pretreatment α-fetoprotein levels were within the normal range. One patient developed HCC 1.7 years after achieving sustained virologic response, and 2 patients developed HCC 3.9 years after achieving sustained virologic response.

### DISCUSSION

We found that in a Western population with chronic hepatitis C and advanced fibrosis, sustained virologic response to antiviral therapy reduces complications of liver disease, especially development of liver failure. This finding is important because the incidence of liver failure among persons with untreated cirrhosis in Europe has been esti-

mated to be 4 times as high as the incidence of HCC (12). Patients with severe liver disease are more likely to both not respond to therapy and have subsequent decompensation. Our finding that therapy provides long-term clinical benefit for patients with a sustained virologic response may help to change attitudes toward screening persons who are at risk for hepatitis C infection. The lack of data on long-term outcomes after treatment has been 1 of the main reasons that such a screening program has not been implemented in the United States (13).

Our finding of a reduction in liver failure contrasts with results of studies from Japan, where the benefit of interferon treatment lies mainly in the prevention of HCC (14, 15). In our sample, the decrease in incidence of HCC was not statistically significant and was less pronounced than the decrease in incidence of liver failure. Among 142 patients with sustained virologic response, 3 developed HCC. A recent report from Italy showed that the incidence of HCC was 0.7% per year among patients with cirrhosis who had sustained virologic response (16). This value is lower than the 5-year incidence of HCC of 9.2% that we found, which corresponds to an annual incidence of 1.8%. In a previous study, we found no HCC among patients with sustained virologic response whom we followed for up to 4.9 years, but this cohort included relatively few patients with advanced fibrosis: 53 patients had severe fibrosis (F3 according to the METAVIR fibrosis scoring system [17]) and 15 had cirrhosis (18). Although we observed no statistically significant reduction in the development of HCC among patients with sustained virologic response compared with those without response, most cases of HCC occurred in the latter group. If the

duration of follow-up had been longer, the differences in HCC development between patients with and those without sustained virologic response might have been more pronounced. The difference between these groups might also have been larger if we had excluded patients with relapse from the study. Because patients with relapse had an undetectable viral load during treatment, their time to complications may be prolonged compared with true nonresponders.

In 2 other reports, 2 Western patients who developed HCC after achieving sustained virologic response both had cirrhosis (19, 20). This may indicate that with further progression of fibrosis, the liver undergoes irreversible changes, leading to an elevated risk for carcinogenesis even when the original noxious factor has been removed. Another explanation may be that these patients have other risk factors. Of the 3 patients in our cohort who had sustained virologic response but developed HCC, 2 had diabetes and were anti–hepatitis B core antigen positive. Both of these factors have been suggested to increase the risk for HCC (21), although the effect of anti–hepatitis B core antigen positivity on development of HCC remains controversial (22–24). Finally, HCC may occur in persons with sustained virologic response, because a small, undetectable HCC was already present before sustained virologic response was achieved.

Previous studies from Japan reported an HCC incidence of 0.7% to 2.5% per year among patients with sustained virologic response and advanced fibrosis or cirrhosis (5, 15, 25, 26). The lowest rate was reported by Okanoue and colleagues (25), who found 4 cases of HCC among 86 patients with advanced fibrosis (82 with F3 and 4 with F4 according to the METAVIR fibrosis scoring system [17]) during 6 years of follow-up. The highest rate was reported by Shiratori and associates (15), who described 11 cases of HCC during 6.8 years of follow-up among 64 patients with sustained virologic response and cirrhosis.

Our study has several limitations. Few events occurred in the sustained virologic response group; the effect of sustained virologic response was therefore only statistically significant in the combined outcome of "any event," which combines potentially disparate effects from the individual outcomes. Because of ongoing improvements in the treatment of chronic hepatitis C, patients who have been treated more recently have a higher chance of sustained virologic response than patients who were treated earlier. Therefore, in this retrospective cohort study, it is inevitable that patients with sustained virologic response have a shorter follow-up than that of nonresponders. However, because patients were censored at the time of their last visit in the Cox regression analysis, a difference in follow-up time would be relevant only if the rate of occurrence of clinical events changed over time: for example, if the incidence of HCC increases dramatically more than 2 years after treatment and most patients with sustained virologic response do not reach 2 years of follow-up. The Kaplan–

Meier curves shown in the **Figure** do not suggest this, however, and indicate instead that the rate of occurrence of clinical events is almost linear. Moreover, subgroup analysis of the patients who were treated after 1998 with combination therapy shows that the difference in occurrence of clinical events between patients with and those without sustained virologic response remains, although their follow-up time is similar. The few events among patients in the sustained virologic response group also mean that the study findings depend heavily on our modeling assumptions, the covariates we included, and the assumption of noninformative censoring. However, we carefully selected all relevant covariates and verified our findings by using different analyses (for example, modeling response to treatment as a time-dependent covariate; see the **Appendix**, available at www.annals.org), and our results did not change when the data were analyzed in a different manner.

Misclassification of response category may have occurred because early polymerase chain reaction tests were less sensitive and no patient samples were available for HCV RNA retesting. However, we believe the risk for misclassification is very small, because studies have found that when samples are retested with recent assays, the samples at the end of follow-up show complete concordance (27, 28). The patients in our study were all classified according to their virologic response at the end of follow-up. Therefore, in our study, responders represent persons with true sustained virologic response.

Not all patients with genotype 1 in our study received 48 weeks of treatment, which is currently regarded as optimal. Therefore, the proportion of patients with sustained virologic response may be lower than that in studies in which all patients with genotype 1 received 48 weeks of treatment. However, this does not affect the validity of our finding that patients with sustained virologic response have a better clinical outcome than those without response.

Finally, the retrospective nature of the study may have led to selection bias. Some patients with severe cirrhosis were probably not considered for treatment and were therefore not included. However, even though this bias may imply that we investigated persons with early cirrhosis, the incidence of clinical events was sufficiently high to show that sustained virologic response decreases risk for events indicative of liver failure.

In conclusion, we found that sustained virologic response after treatment with interferon or pegylated interferon with or without ribavirin is associated with a reduction in clinical events, mainly liver failure, in patients with chronic hepatitis C and advanced fibrosis. These findings make clear the importance of developing treatment regimens that are simple to adhere to and that maximize the probability of sustained virologic response in patients with chronic hepatitis C infection.

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## APPENDIX

### Covariate and Model Selection Strategies

In our logistic regression models, we observed multiple collinearity between fibrosis stage and bilirubin level, platelet count, and albumin level, presumably because these factors reflect the severity of liver disease. Therefore, we developed 2 separate models: 1 that included fibrosis and 1 that included bilirubin level, platelet count, and albumin level. We used the latter model because it had the lowest Akaike information criterion score, provided the best fit to the data, and had good discrimination (Hosmer–Lemeshow goodness-of-fit test, $P > 0.35$; area under the receiver-operating characteristic curve, 0.83).

In our proportional hazard models, we could not adjust for all risk factors for all events because few events occurred; we therefore identified factors that correlated highly with each other (that is, were multicollinear), then compared separate models with each collinear variable (or set of variables) by using the overall score test (PROC PHREG, with the subcommand BEST SUBSET in SAS software) and the Akaike information criterion method. Treatment with ribavirin or pegylated interferon versus standard interferon were not included in the final model because of multiple collinearity with treatment period, by which the model was stratified. The covariates "treatment duration" and "genotype" were not associated with any end point in the univariate proportional hazards analysis and, when included in the model, did not improve model fit; therefore, neither were considered in the final model. Viral load at the start of therapy was not included in the model because data were missing in 31.5% of cases and because sustained virologic response reflects the most recent measure of the viral load. Estimates of hazard did not change when response to treatment was modeled as a time-dependent covariate to represent the ability of patients undergoing more than 1 treatment course to change their status from nonresponders to responders in sequential courses. Finally, fibrosis and the covariates bilirubin level, platelet count, and albumin level were collinear; as with the logistic regression model, we developed 2 separate models, which included fibrosis or the covariates bilirubin level, platelet count, and albumin level. The latter had the lowest Akaike information criterion score, provided the best fit to the data, and was chosen as the final model.

Tests of the assumption of proportionality were not violated for any of the covariates except anti–hepatitis B core antigen positivity (see Statistical Analysis).

*Appendix Figure.* Relationship of overall, liver-related, and non–liver-related deaths among nonresponders.
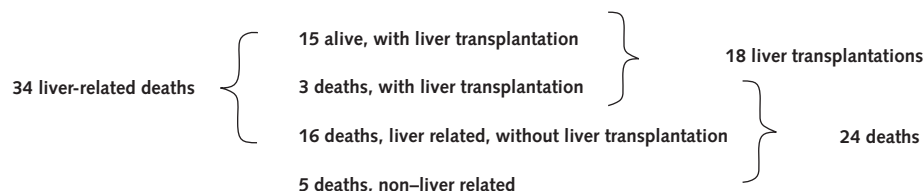


Liver transplantation counted as liver-related death at the time of transplantation, but patients who were alive after liver transplantation were regarded as alive in the analysis of overall death.

**Appendix Table.** Clinical Outcomes, by Response to Treatment

| Outcome | Patients with Sustained Virologic Response | | | Patients without Sustained Virologic Response | | | Hazard Ratio (95% CI) | | P Value* |
|---|---|---|---|---|---|---|---|---|---|
| | Events, *n* | Observation Period, *patient-years* | Events per Observation Period, *n* | Events, *n* | Observation Period, *patient-years* | Events per Observation Period, *n* | Unadjusted | Adjusted | |
| **Any event** | | | | | | | | | |
| Overall | 4 | 280 | 143 | 83 | 1107 | 750 | – | – | – |
| Sustained virologic response | – | – | – | – | – | – | 0.20 (0.07–0.55) | 0.20 (0.07–0.58) | 0.003 |
| Age | – | – | – | – | – | – | 1.05 (1.03–1.08) | 1.57 (1.20–2.06) | 0.001 |
| Male sex | – | – | – | – | – | – | 1.32 (0.83–2.13) | 1.71 (0.99–2.93) | 0.052 |
| Previous nonresponse | – | – | – | – | – | – | 0.93 (0.57–1.53) | 0.51 (0.23–1.11) | 0.09 |
| Treatment duration | – | – | – | – | – | – | 0.99 (0.98–1.01) | – | – |
| Type of therapy | | | | | | | | | |
| Pegylated interferon | – | – | – | – | – | – | 0.45 (0.24–0.86) | – | – |
| Ribavirin | – | – | – | – | – | – | 1.56 (0.93–2.63) | – | – |
| Fibrosis stage | – | – | – | – | – | – | 1.96 (1.40–2.74) | – | – |
| Genotype 1 | – | – | – | – | – | – | 1.13 (0.63–2.02) | – | – |
| Bilirubin level | – | – | – | – | – | – | 2.42 (1.77–3.32) | 1.33 (0.98–1.80) | 0.07 |
| Albumin level | – | – | – | – | – | – | 0.01 (0.00–0.08) | 0.61 (0.27–1.38) | 0.23 |
| Platelet count | – | – | – | – | – | – | 0.11 (0.05–0.23) | 0.90 (0.85–0.96) | 0.001 |
| Viral load | – | – | – | – | – | – | 1.08 (0.70–1.66) | – | – |
| Treatment center | | | | | | | | | |
| Center 1 | – | – | – | – | – | – | 1.00 (reference) | 1.00 (reference) | – |
| Center 2 | – | – | – | – | – | – | 3.07 (1.67–5.64) | 4.97 (2.03–12.2) | 0.001 |
| Center 3 | – | – | – | – | – | – | 3.07 (1.60–5.91) | 1.56 (0.71–3.41) | 0.27 |
| Center 4 | – | – | – | – | – | – | 1.78 (1.02–3.11) | 1.00 (0.54–1.84) | 0.99 |
| Center 5 | – | – | – | – | – | – | 0.66 (0.16–2.74) | 1.13 (0.24–5.45) | 0.88 |
| Treatment period | – | – | – | – | – | – | 1.40 (0.83–2.34) | – | – |
| | | | | | | | | | |
| **Overall death** | | | | | | | | | |
| Overall | 2 | 281 | 71 | 24 | 1243 | 193 | – | – | – |
| Sustained virologic response | – | – | – | – | – | – | 0.44 (0.10–1.87) | 0.31 (0.07–1.38) | 0.124 |
| Age | – | – | – | – | – | – | 1.07 (1.02–1.11) | 2.43 (1.49–3.96) | <0.001 |
| Male sex | – | – | – | – | – | – | 1.59 (0.64–3.95) | 2.00 (0.71–5.65) | 0.190 |
| Previous nonresponse | – | – | – | – | – | – | 0.39 (0.12–1.30) | 0.08 (0.01–0.75) | 0.027 |
| Treatment duration | – | – | – | – | – | – | 1.00 (0.98–1.03) | – | – |
| Type of therapy | | | | | | | | | |
| Pegylated interferon | – | – | – | – | – | – | 0.54 (0.16–1.84) | – | – |
| Ribavirin | – | – | – | – | – | – | 2.53 (0.95–6.76) | – | – |
| Fibrosis stage | – | – | – | – | – | – | 1.86 (1.01–3.44) | – | – |
| Genotype 1 | – | – | – | – | – | – | 1.06 (0.39–2.92) | – | – |
| Bilirubin level | – | – | – | – | – | – | 2.90 (1.85–4.54) | 2.19 (1.26–3.79) | 0.006 |
| Albumin level | – | – | – | – | – | – | 0.11 (0.00–5.72) | 1.23 (0.32–4.68) | 0.76 |
| Platelet count | – | – | – | – | – | – | 0.16 (0.04–0.55) | 0.95 (0.86–1.04) | 0.27 |
| Viral load | – | – | – | – | – | – | 1.18 (0.52–2.70) | – | – |
| Treatment center | | | | | | | | | |
| Center 1 | – | – | – | – | – | – | 1.00 (reference) | 1.00 (reference) | – |
| Center 2 | – | – | – | – | – | – | 1.69 (0.54–5.35) | 9.25 (1.22–70.1) | 0.031 |
| Center 3 | – | – | – | – | – | – | 4.07 (1.62–10.2) | 1.22 (0.34–4.37) | 0.77 |
| Center 4 | – | – | – | – | – | – | 0.60 (0.17–2.15) | 0.29 (0.07–1.20) | 0.087 |
| Center 5 | – | – | – | – | – | – | 0 | 0 | <0.001 |
| Treatment period | – | – | – | – | – | – | 2.19 (0.83–5.82) | – | – |
| | | | | | | | | | |
| **Liver-related death†** | | | | | | | | | |
| Overall | 1 | 281 | 36 | 34 | 1200 | 283 | – | – | – |
| Sustained virologic response | – | – | – | – | – | – | 0.14 (0.02–1.03) | 0.19 (0.02–1.44) | 0.107 |
| Age | – | – | – | – | – | – | 1.04 (1.00–1.08) | 1.58 (1.04–2.41) | 0.032 |
| Male sex | – | – | – | – | – | – | 1.05 (0.51–2.14) | 1.17 (0.51–2.69) | 0.71 |
| Previous nonresponse | – | – | – | – | – | – | 0.91 (0.41–2.01) | 0.60 (0.15–2.39) | 0.47 |
| Treatment duration | – | – | – | – | – | – | 0.99 (0.97–1.01) | – | – |
| Type of therapy | | | | | | | | | |
| Pegylated interferon | – | – | – | – | – | – | 0.48 (0.17–1.39) | – | – |
| Ribavirin | – | – | – | – | – | – | 2.07 (0.91–4.74) | – | – |
| Fibrosis stage | – | – | – | – | – | – | 1.63 (1.00–2.65) | – | – |
| Genotype 1 | – | – | – | – | – | – | 1.40 (0.53–3.74) | – | – |
| Bilirubin level | – | – | – | – | – | – | 3.11 (2.09–4.62) | 1.67 (1.09–2.56) | 0.018 |
| Albumin level | – | – | – | – | – | – | 0.00 (0.00–0.08) | 0.53 (0.17–1.63) | 0.27 |
| Platelet count | – | – | – | – | – | – | 0.05 (0.01–0.17) | 0.88 (0.79–0.98) | 0.018 |
| Viral load | – | – | – | – | – | – | 0.80 (0.41–1.56) | – | – |
| Treatment center | | | | | | | | | |
| Center 1 | – | – | – | – | – | – | 1.00 (reference) | 1.00 (reference) | – |
| Center 2 | – | – | – | – | – | – | 3.15 (1.12–8.89) | 5.35 (1.04–27.5) | 0.045 |
| Center 3 | – | – | – | – | – | – | 6.00 (2.26–15.9) | 1.83 (0.48–6.91) | 0.37 |
| Center 4 | – | – | – | – | – | – | 2.89 (1.19–7.00) | 1.45 (0.52–4.04) | 0.48 |
| Center 5 | – | – | – | – | – | – | 1.65 (0.21–13.1) | 1.95 (0.17–22.0) | 0.59 |
| Treatment period | – | – | – | – | – | – | 3.51 (1.40–8.82) | – | – |

| Outcome | Patients with Sustained Virologic Response | | | Patients without Sustained Virologic Response | | | Hazard Ratio (95% CI) | | P Value* |
|---|---|---|---|---|---|---|---|---|---|
| | Events, *n* | Observation Period, *patient-years* | Events per Observation Period, *n* | Events, *n* | Observation Period, *patient-years* | Events per Observation Period, *n* | Unadjusted | Adjusted | |
| **Non–liver-related death‡** | | | | | | | | | |
| Overall | 1 | 281 | 36 | 5 | 1245 | 40 | | | |
| Sustained virologic response | – | – | – | – | – | – | 1.21 (0.14–10.6) | – | – |
| Age | – | – | – | – | – | – | 1.05 (0.96–1.15) | – | – |
| Male sex | – | – | – | – | – | – | 2.46 (0.28–21.1) | – | – |
| Previous nonresponse | – | – | – | – | – | – | 0.03 (0.00–91.4) | – | – |
| Treatment duration | – | – | – | – | – | – | 1.02 (0.97–1.06) | – | – |
| Type of therapy | | | | | | | | | |
| Peginterferon | – | – | – | – | – | – | 0.04 (0.00–429.4) | – | – |
| Ribavirin | – | – | – | – | – | – | 0.71 (0.06–8.67) | – | – |
| Fibrosis stage | – | – | – | – | – | – | 2.80 (0.54–16.6) | – | – |
| Genotype 1 | – | – | – | – | – | – | 0.47 (0.08–2.85) | – | – |
| Bilirubin level | – | – | – | – | – | – | 2.05 (0.45–9.36) | – | – |
| Albumin level | – | – | – | – | – | – | 21.3 (0.00–125 039) | – | – |
| Platelet count | – | – | – | – | – | – | 1.07 (0.13–8.70) | – | – |
| Viral load | – | – | – | – | – | – | 5.95 (0.38–93.9) | – | – |
| Treatment center | | | | | | | | | |
| Center 1 | – | – | – | – | – | – | 1.00 (reference) | – | – |
| Center 2 | – | – | – | – | – | – | 0 | – | – |
| Center 3 | – | – | – | – | – | – | 3.29 (0.57–18.8) | – | – |
| Center 4 | – | – | – | – | – | – | 0 | – | – |
| Center 5 | – | – | – | – | – | – | 0 | – | – |
| Treatment period | – | – | – | – | – | – | 0.62 (0.05–7.43) | – | – |
| **Liver failure§** | | | | | | | | | |
| Overall | 0 | 281 | 0 | 42 | 1150 | 365 | | | |
| Sustained virologic response | – | – | – | – | – | – | 0.03 (0.00–0.91) | – | – |
| Age | – | – | – | – | – | – | 1.04 (1.01–1.08) | 1.39 (0.93–2.07) | 0.107 |
| Male sex | – | – | – | – | – | – | 1.00 (0.52–1.91) | 1.21 (0.56–2.62) | 0.63 |
| Previous nonresponse | – | – | – | – | – | – | 0.72 (0.33–1.55) | 0.23 (0.07–0.82) | 0.023 |
| Treatment duration | – | – | – | – | – | – | 0.99 (0.96–1.00) | – | – |
| Type of therapy | | | | | | | | | |
| Pegylated interferon | – | – | – | – | – | – | 0.49 (0.20–1.18) | – | – |
| Ribavirin | – | – | – | – | – | – | 1.30 (0.61–2.78) | – | – |
| Fibrosis stage | – | – | – | – | – | – | 2.39 (1.39–4.12) | – | – |
| Genotype 1 | – | – | – | – | – | – | 2.37 (0.82–6.83) | – | – |
| Bilirubin | – | – | – | – | – | – | 3.08 (2.04–4.64) | 1.68 (1.10–2.55) | 0.016 |
| Albumin | – | – | – | – | – | – | 0.00 (0.00–0.03) | 0.50 (0.14–1.80) | 0.28 |
| Platelet count | – | – | – | – | – | – | 0.04 (0.01–0.15) | 0.84 (0.76–0.94) | 0.003 |
| Viral load | – | – | – | – | – | – | 1.17 (0.64–2.16) | – | – |
| Treatment center | | | | | | | | | |
| Center 1 | – | – | – | – | – | – | 1.00 (reference) | 1.00 (reference) | – |
| Center 2 | – | – | – | – | – | – | 3.08 (1.37–6.95) | 10.3 (2.97–35.4) | <0.001 |
| Center 3 | – | – | – | – | – | – | 1.81 (0.65–5.06) | 0.41 (0.11–1.58) | 0.196 |
| Center 4 | – | – | – | – | – | – | 1.17 (0.50–2.77) | 0.60 (0.23–1.57) | 0.30 |
| Center 5 | – | – | – | – | – | – | 0 | 0 | <0.001 |
| Treatment period | – | – | – | – | – | – | 1.18 (0.56–2.50) | – | – |
| **Hepatocellular carcinoma** | | | | | | | | | |
| Overall | 3 | 280 | 107 | 32 | 1157 | 277 | | | |
| Sustained virologic response | – | – | – | – | – | – | 0.46 (0.14–1.52) | 0.46 (0.12–1.70) | 0.25 |
| Age | – | – | – | – | – | – | 1.08 (1.04–1.13) | 2.16 (1.42–3.30) | <0.001 |
| Male sex | – | – | – | – | – | – | 1.93 (0.85–4.43) | 3.44 (1.35–0.90) | 0.010 |
| Previous nonresponse | – | – | – | – | – | – | 1.35 (0.66–2.76) | 0.93 (0.30–2.88) | 0.91 |
| Treatment duration | – | – | – | – | – | – | 1.01 (0.99–1.03) | – | – |
| Type of therapy | | | | | | | | | |
| Pegylated interferon | – | – | – | – | – | – | 0.48 (0.17–1.39) | – | – |
| Ribavirin | – | – | – | – | – | – | 1.63 (0.72–3.66) | – | – |
| Fibrosis stage | – | – | – | – | – | – | 1.56 (0.97–2.50) | – | – |
| Genotype 1 | – | – | – | – | – | – | 0.92 (0.39–2.19) | – | – |
| Bilirubin | – | – | – | – | – | – | 1.72 (0.90–3.28) | 1.00 (0.53–1.89) | 0.99 |
| Albumin | – | – | – | – | – | – | 0.08 (0.00–3.32) | 0.48 (0.13–1.73) | 0.25 |
| Platelet count | – | – | – | – | – | – | 0.24 (0.08–0.71) | 0.95 (0.88–1.03) | 0.25 |
| Viral load | – | – | – | – | – | – | 1.24 (0.63–2.41) | – | – |
| Treatment center | | | | | | | | | |
| Center 1 | – | – | – | – | – | – | 1.00 (reference) | 1.00 (reference) | – |
| Center 2 | – | – | – | – | – | – | 3.89 (1.47–10.3) | 4.85 (1.21–19.4) | 0.026 |
| Center 3 | – | – | – | – | – | – | 4.73 (1.76–12.7) | 5.16 (1.38–19.3) | 0.015 |
| Center 4 | – | – | – | – | – | – | 2.02 (0.82–5.00) | 1.49 (0.56–4.00) | 0.43 |
| Center 5 | – | – | – | – | – | – | 2.35 (0.51–10.7) | 4.82 (0.80–29.1) | 0.086 |
| Treatment period | – | – | – | – | – | – | 1.43 (0.64–3.21) | – | – |

* For adjusted hazard ratios.
† Includes 17 deaths (1 patient with and 16 without sustained virologic response) and 18 patients who had liver transplantation (all of whom did not have sustained virologic response). Patients with liver transplantations are included in "Liver-related death" but not in "Overall death," unless a patient died after liver transplantation (as occurred in 3 patients without response). See also the **Appendix Figure.**
‡ Too few non–liver-related deaths occurred to assess the effect of sustained virologic response on non–liver-related death in multivariable analysis.
§ The effect of sustained virologic response on liver failure could not be quantified in multivariable analysis, because no patient with sustained virologic response developed liver failure during follow-up.