ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

A Sustained Virologic Response Reduces Risk of All-Cause Mortality in Patients With Hepatitis C

LISA I. BACKUS, DEREK B. BOOTHROYD, BARBARA R. PHILLIPS, PAMELA BELPERIO, JAMES HALLORAN, and LARRY A. MOLE

Center for Quality Management in Public Health, Veterans Affairs Palo Alto Health Care System, Palo Alto, California

See related article, Freedman MD et al, on page 1961 in *Gastroenterology*.

BACKGROUND & AIMS: The effectiveness of hepatitis C virus (HCV) treatment with pegylated interferon and ribavirin usually is evaluated by the surrogate end point of sustained virologic response (SVR), although the ultimate goal of antiviral treatment is to reduce mortality. The impact of SVR on all-cause mortality is not well documented by HCV genotype or in populations in routine medical practice with substantial comorbidities. **METHODS:** From the US Department of Veterans Affairs (VA), we identified all patients infected with HCV genotypes 1, 2, or 3, without human immunodeficiency virus co-infection or hepatocellular carcinoma before HCV treatment with pegylated interferon and ribavirin, who started HCV treatment from January 2001 to June 2007, stopped treatment by June 2008, and had a posttreatment HCV RNA test result of SVR or no SVR. Mortality data from VA and non-VA sources were available through 2009. **RESULTS:** HCV genotypes 1, 2, or 3 cohorts consisted of 12,166, 2904, and 1794 patients, respectively, with SVR rates of 35%, 72%, and 62%, respectively. Each cohort had high rates of comorbidities. During a median follow-up period of approximately 3.8 years, 1119 genotype-1, 220 genotype-2, and 196 genotype-3 patients died. In genotype-specific multivariate survival models that controlled for demographic factors, comorbidities, laboratory characteristics, and treatment characteristics, an SVR was associated with substantially reduced mortality risk for each genotype (genotype-1 hazard ratio, 0.70; $P < .0001$; genotype-2 hazard ratio, 0.64; $P = .006$; genotype-3 hazard ratio, 0.51; $P = .0002$). **CONCLUSIONS: An SVR reduced mortality among patients infected with HCV of genotypes 1, 2, or 3 who were being treated by routine medical practice and had substantial comorbidities.**

Keywords: Liver Disease; Antiviral Therapy; Efficacy; IFN.

The effectiveness of hepatitis C virus (HCV) antiviral treatment usually is evaluated by the surrogate end point of sustained virologic response (SVR); however, the ultimate goal of antiviral treatment is reduced mortality. Most of the prior research on the long-term effects of SVR has concentrated on liver-related morbidity and liver-related mortality.[1] Studies limited to liver-related mortality may be affected by problems in coding cause of death, which have been identified for other conditions.[2] It also is possible that HCV places a patient at increased mortality risk from nonliver causes; for example, HCV has been associated with increased atherosclerosis even after adjusting for traditional cardiovascular risk factors.[3] Thus, studies limited to liver-related mortality may inaccurately estimate the clinical impact of SVR.

Only a small number of studies have considered the association between SVR and all-cause mortality.[4–8] Conducted in Canada, Europe, and Japan, it is unclear whether the results of these studies apply to the US population given differences in prevailing genotype, level of comorbidities, and observed differences in the natural history of HCV, particularly with regard to a much higher incidence of hepatocellular carcinoma in Japan.[9] In addition, several of these studies included only patients with advanced fibrosis or cirrhosis so these study results may not apply to patients without advanced liver disease.[6–8] Four of these 5 studies found significant mortality reductions with SVR in unadjusted analyses[4–7] and 1 study found a significant reduction in mortality with SVR in adjusted analyses when compared with untreated patients.[4] These studies could adjust for only a small number of potential confounders in multivariate analyses because each observed a small number of deaths. Adjustment for potential confounders is important because patients who did not achieve SVR may have higher rates of unfavorable factors such as obesity and diabetes, which may underlie the lack of treatment response[10,11] and also may lead to higher mortality rates.[12]

Most Americans infected with HCV were born between 1945 and 1964 and became infected in the 1960s and 1970s.[13] As this population ages, they will develop age-related conditions such as coronary artery disease, diabetes, and hypertension that will substantially increase the risk of death. In such a population, mortality from non–liver-related causes may overwhelm the clinical significance of any reduction in liver-related mortality, and clinicians may defer treatment for HCV given uncertainty about the long-term clinical impact of SVR. Given the large size of the US popu-

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GT, genotype; HCV, hepatitis C virus; HTN, hypertension; ICD-9, International Classification of Diseases, 9th revision; PEG-IFN, pegylated interferon alfa; SVR, sustained virologic response; VA, Department of Veterans Affairs.

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lation infected with HCV, it is important to understand the impact of SVR on all-cause mortality in populations with substantial comorbidities.

The Department of Veterans Affairs (VA) cares for more than 150,000 patients with HCV annually and is the largest provider of health care to HCV-infected individuals in the United States.[14] The VA population with HCV has high rates of comorbidities, which may shorten survival independent of the patient's HCV.[14,15] We used the large VA population and the unique opportunity it provides to examine the impact of SVR on all-cause mortality by HCV genotype in a real-world population with substantial comorbidities.

Methods

We used data automatically extracted from the VA's electronic medical record into the Clinical Case Registry to identify veterans with HCV receiving care at any VA medical facility.[16] A patient was included in the primary investigation if the following criteria were met: (1) had HCV genotype (GT) 1, 2, or 3; (2) started pegylated interferon (PEG-IFN)/ribavirin between January 20, 2001, and June 30, 2007; (3) stopped PEG-IFN/ribavirin treatment by June 30, 2008; and (4) had a HCV RNA test result after the treatment end date that allowed categorization of the virologic response as SVR or not. Patients were excluded if they had human immunodeficiency virus co-infection or a diagnosis of hepatocellular carcinoma before the start of treatment. The treatment end date was defined as the latest date covered by any PEG-IFN prescription. In a secondary sensitivity analysis, we included patients who met the first 3 inclusion criteria, but had no post-treatment HCV RNA test result.

Patients with a detectable HCV RNA level at any time after the treatment end date were considered nonresponders (no SVR). Patients were considered to have an SVR if they had an undetectable HCV RNA level on all HCV RNA tests after the treatment end date including at least one test 12 weeks or more after that date. We allowed a test 12 weeks or more after the treatment end date because 98% to 99% of relapses occur within 12 weeks after therapy cessation[17,18] and because of the scheduling realities of routine medical care. Patients with undetectable HCV RNA results after the treatment end date but no test 12 weeks or more after that date were excluded from the analysis. In a secondary sensitivity analysis, we included as SVR only those patients with at least one HCV RNA test 24 weeks or later after the treatment end date.

The following patient demographic variables were measured: age at treatment start date, sex, and race/ethnicity. Race/ethnicity was unknown in 16% of cases. Baseline values for height, weight, and all laboratory tests were defined as the result within 1 year before and closest to the treatment start date with the exception of HCV genotype and hepatitis B virus co-infection, which used the most recent result. Creatinine clearance was calculated using the Cockcroft–Gault formula.[19]

We determined the presence of selected baseline comorbidities that may affect HCV treatment response and survival.[11,20] By using all International Classification of Diseases, 9th revision (ICD-9) codes before the treatment start date, we categorized a patient as having a history of coronary artery disease, cancer, congestive heart failure, cirrhosis, chronic obstructive pulmonary disease, cerebrovascular disease, hypertension (HTN), or schizophrenia based on the occurrence of 1 inpatient discharge diagnosis code, 1 problem list code, or 2 outpatient codes (on different dates). A patient was categorized as having diabetes based on ICD-9 codes, a baseline fasting glucose level of 126 mg/dL or higher, or 2 casual blood glucose readings of 200 mg/dL or higher in the year before treatment. Patients with pertinent ICD-9 codes within 1 year before the treatment start date were categorized as having recent alcohol abuse, anxiety disorder, depression, hard drug use (opiates, cocaine, or amphetamines), posttraumatic stress disorder, or socioeconomic status instability (homelessness, poverty, or unemployment). Tobacco use was characterized as recent (a diagnosis code within 1 y before the treatment start date), remote (a previous diagnosis code but none recent), or none (no relevant diagnosis codes).

Treatment duration was calculated from the cumulative days' supply of PEG-IFN and categorized as less than 60%, 60% to 79%, 80% to 99%, 100% to 124%, and 125% or more of the recommended treatment duration (48 weeks for genotype 1, 24 weeks for genotypes 2 and 3).[21] Patients were considered to have received multiple treatment courses (separated by a gap) if the treatment duration calculated from the treatment start and end dates was more than 45 days longer than the cumulative PEG-IFN days' supply. We determined whether a patient received a granulocyte or erythrocyte stimulating agent while on treatment.

Mortality data were available through December 31, 2009, from the VA Vital Status File, which draws from the Medicare Vital Status Files, Social Security Administration Death Master Files, VA Beneficiary Identification Records Locator Subsystem Death File, and VA Medical Records, and compares favorably with the National Death Index.[22] Because the mortality data are national and drawn from non-VA as well as VA sources, it is reasonable to assume that no patients are lost to follow-up evaluation with respect to measurement of survival.

To avoid bias, we measured survival from the informative post-treatment test date rather than the start or end of treatment. The completion of a treatment course and receipt of a posttreatment HCV RNA test at least 12 (or 24) weeks after the end of treatment for determination of SVR necessarily require longer survival. For the sensitivity analysis including patients without posttreatment tests, we measured survival time beginning from the treatment end date.

Statistical Analysis

Univariate comparisons of responder and nonresponder characteristics for each genotype used the Pearson chi-square test for categoric variables and *t* tests for continuous variables. We fitted univariate and multivariate proportional hazards models within each of the 3 genotypes to assess survival in patients with and without SVR. Multivariate survival models included demographic, laboratory, comorbidity, and treatment variables as well as treatment response.

We considered multiple forms of continuous variables for the multivariate models. After assessing the fit and testing for nonproportional hazards in univariate survival models among patients with GT1, we selected the raw value or, for some variables, a log-transformed value. We also constructed and included sets of categoric variables.

There was evidence of nonproportional hazards for the race/ethnicity variable, likely because the longer a patient is in VA care, the less likely that data on race and ethnicity are missing. To resolve this issue, our primary survival models were stratified by race/ethnicity.

For sensitivity analysis, secondary multivariate models were run as follows: (1) considering as SVR only those patients with at least one

Table 1. Key Baseline Patient Characteristics Before PEG-IFN/Ribavirin

	GT1 (n = 12,166)	GT2 (n = 2904)	GT3 (n = 1794)
Male sex, *%*	96	96	96
Mean age, *y* (SD)	51.9 (5.7)	53.0 (6.2)	51.0 (5.8)
Race/ethnicity, *%*			
African American	23	6	3
Hispanic	6	6	6
Other/multiple/missing	18	20	20
White	53	68	71
Mean albumin level, *g/dL* (SD)	4.0 (0.4)	4.1 (0.4)	4.0 (0.4)
Mean ALT level, *U/mL* (SD)	90.4 (72.2)	95.7 (87.2)	110.9 (82.9)
Mean AST level, *U/mL* (SD)	66.3 (51.0)	64.4 (54.1)	79.3 (55.9)
Mean bilirubin level, *mg/dL* (SD)	0.8 (0.5)	0.7 (0.4)	0.8 (0.4)
Mean BMI kg/m^2 (SD)	29.2 (5.2)	29.3 (5.4)	28.8 (5.2)
Mean creatinine level, *mg/dL* (SD)	1.0 (0.4)	1.0 (0.3)	1.0 (0.2)
Median HCV RNA, $\times 10^6$ *IU/mL* (IQR)	1.0 (0.5–3.5)	1.8 (0.5–5.0)	0.78 (0.3–2.6)
Mean platelets, $\times 10^9/L$ (SD)	207.7 (71.2)	212.3 (69.8)	195.2 (72.8)
Comorbidities, *%*			
CAD	13	13	10
Cirrhosis	13	9	16
COPD	14	16	15
Diabetes	21	17	16
HTN	53	51	42
Tobacco use, *%*			
Recent	33	36	41
Remote	19	16	17

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

HCV RNA test 24 weeks or later after the treatment end date; (2) excluding patients with a diagnosis of cirrhosis before treatment; and (3) including (as nonresponders) patients who were alive at the end of treatment but did not have a posttreatment HCV RNA test. The rationale for treating patients without a posttreatment test as nonresponders was that they generally had shortened treatment courses unlikely to result in SVR and had detectable HCV RNA on their last on-treatment test. Nonetheless, some patients without a posttreatment HCV RNA test may have had an unobserved SVR, including them as nonresponders would tend to underestimate the effect of SVR.

Data were analyzed using SAS software version 9.1 (SAS Institute, Cary, NC).

The protocol was approved by the Stanford University Institutional Review Board, the VA Palo Alto Health Care System Research and Development Committee, and the VA Public Health Strategic Healthcare Group Clinical Case Registry Data Use Committee.

Results

We identified 22,942 patients who started and stopped treatment with PEG-IFN/ribavirin by the date criteria. Patients were excluded from the primary cohort for human immunodeficiency virus co-infection (649), hepatocellular carcinoma before treatment (64), an undetectable posttreatment HCV RNA but no test 12 weeks or more after the treatment end date (380), and no posttreatment HCV RNA test (4985). Sixty-five percent of the patients with no posttreatment HCV RNA test had a treatment duration of less than 60% of that recommended for their genotype and 77% of such patients had detectable HCV RNA at their last on-treatment test. It is likely their physicians already had classified them as nonresponders and did not order a posttreatment test.

Key patient and treatment characteristics for the remaining 16,864 patients who comprise the primary GT1, GT2, and GT3 cohorts appear in Table 1. All measured characteristics are available in the Appendix. The cohorts were overwhelmingly male (96%) with an average age in the 50s. Patients had baseline laboratory results with mean values in the normal range for albumin, bilirubin, creatinine, hemoglobin, platelets, and sodium. On average, the cohort patients had both increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, with higher ALT levels. GT3 patients had the highest rate of cirrhosis at 16%, followed by GT1 at 13% and GT2 at 9%. Cohort patients had substantial rates of other comorbidities that potentially impacted survival including coronary artery disease, chronic obstructive pulmonary disease, diabetes, and HTN, as well as recent diagnoses of alcohol abuse, depression, hard drug use, and tobacco use.

The SVR rates for GT1, GT2, and GT3 patients were 35%, 72%, and 62%, respectively. In the sensitivity analysis including the 4985 patients without a posttreatment HCV RNA as nonresponders (4211 GT1, 448 GT2, and 326 GT3), the intention-to-treat SVR rates were 26% for GT1, 62% for GT2, and 52% for GT3.

There were statistically significant although generally numerically small differences between nonresponders and responders on many baseline patient and treatment characteristics (Table 2). For characteristics most directly related to liver health, the pattern of differences between nonresponders and responders was the same for each of the 3 genotype cohorts. Nonresponders had lower albumin levels, higher bilirubin levels, and lower platelet counts than re-

Table 2. Baseline Characteristics by Treatment Response

	GT1			GT2			GT3		
	SVR (n = 4248)	No SVR (n = 7918)	*P*	SVR (n = 2089)	No SVR (n = 815)	*P*	SVR (n = 1097)	No SVR (n = 697)	*P*
Patient characteristics									
Sex, male	95%	96%	<.0001	96%	97%	.03	96%	97%	.15
Mean age, *y* (SD)	51.3 (5.9)	52.0 (5.6)	<.0001	52.8 (6.2)	53.4 (6.3)	.009	50.8 (6.0)	51.4 (5.5)	.01
Race/ethnicity			<.0001			.07			.24
African American	17%	27%		5%	7%		3%	3%	
Hispanic	5%	6%		6%	7%		5%	7%	
Other/multiple/missing	18%	18%		21%	17%		22%	19%	
White	60%	49%		67%	69%		70%	71%	
Mean albumin level, *g/dL* (SD)	4.1 (0.4)	4.0 (0.4)	<.0001	4.1 (0.4)	4.0 (0.5)	<.0001	4.1 (0.4)	4.0 (0.5)	<.0001
AST level, *U/L*			<.0001			.57			<.0001
≤30	18%	14%		25%	27%		14%	9%	
31–60	45%	46%		39%	37%		40%	31%	
61–90	19%	20%		16%	15%		21%	23%	
>90	18%	20%		20%	21%		25%	38%	
AST/ALT ratio			<.0001			<.0001			<.0001
<0.6	33%	21%		33%	27%		30%	22%	
0.6–0.79	35%	31%		33%	30%		35%	32%	
0.8–0.99	19%	24%		18%	19%		21%	19%	
1.0–1.19	8%	13%		10%	13%		8%	14%	
≥1.2	6%	11%		7%	11%		5%	12%	
Mean bilirubin level, *mg/dL* (SD)	0.7 (0.5)	0.8 (0.5)	<.0001	0.7 (0.4)	0.8 (0.4)	.01	0.7 (0.4)	0.8 (0.4)	<.0001
BMI, kg/m^2			.001			.04			.31
<25	19%	16%		18%	15%		22%	19%	
25–29	40%	41%		41%	40%		40%	41%	
≥30	42%	43%		41%	46%		38%	40%	
Creatinine clearance, *mL/min*			.34			.53			.08
≥90	82%	82%		80%	82%		82%	85%	
60–89	17%	17%		19%	17%		18%	14%	
<60	1%	1%		1%	1%		1%	1%	
HBV co-infection	1%	1%	.62	1%	1%	.97	2%	2%	.32
HCV RNA ≥500,000 IU/mL	70%	82%	<.0001	78%	83%	.009	64%	68%	.09
Hemoglobin level <13 g/dL male; <12 g/dL female	4%	6%	.0005	5%	6%	.15	2%	5%	.0006
Platelets, $\times 10^9/L$			<.0001			<.0001			<.0001
<100	3%	7%		3%	8%		5%	17%	
100–149	11%	16%		12%	18%		15%	20%	
≥150	86%	76%		85%	75%		80%	63%	
Sodium level <136 meg/L	8%	9%	.50	11%	9%	.21	8%	10%	.17
Comorbidities									
CAD	11%	14%	<.0001	13%	14%	.43	9%	11%	.27
Cancer	3%	3%	.97	3%	3%	.62	3%	3%	.60
CHF	2%	2%	.43	2%	2%	.27	2%	2%	.99
Cirrhosis	9%	15%	<.0001	7%	12%	<.0001	12%	20%	<.0001
COPD	14%	14%	.39	16%	18%	.27	15%	15%	.72
CVD	1%	1%	.42	1%	1%	.44	1%	1%	.76
Diabetes	16%	23%	<.0001	16%	19%	.03	14%	19%	.003
HTN	49%	55%	<.0001	50%	53%	.10	41%	44%	.22
Schizophrenia	7%	9%	.002	8%	7%	.35	8%	5%	.004
Recent diagnoses									
Alcohol abuse	23%	24%	.24	23%	24%	.55	25%	32%	.003
Anxiety disorder	17%	17%	.78	17%	18%	.43	16%	17%	.66
Depression	36%	35%	.42	35%	36%	.88	37%	38%	.57
Hard drug use	11%	12%	.05	10%	14%	.002	13%	15%	.17
PTSD	15%	17%	.04	17%	20%	.13	13%	17%	.03
SES instability	18%	19%	.55	18%	17%	.59	16%	21%	.003
Tobacco use			.0002			.90			.50
No prior	46%	50%		48%	47%		42%	44%	
Recent	35%	32%		36%	36%		42%	39%	
Remote	18%	19%		16%	17%		16%	17%	

Table 2. Continued

	GT1			GT2			GT3		
	SVR (n = 4248)	No SVR (n = 7918)	*P*	SVR (n = 2089)	No SVR (n = 815)	*P*	SVR (n = 1097)	No SVR (n = 697)	*P*
Treatment characteristics									
Percentage of recommended PEG-IFN duration			<.0001			<.0001			<.0001
<60% (<29 wk GT1; <15 wk GT2/3)	7%	45%		4%	32%		3%	24%	
60%–79% (29–38 wk GT1; 15–19 wk GT2/3)	4%	10%		4%	6%		3%	6%	
80%–99% (39–47 wk GT1; 20–23 wk GT2/3)	12%	8%		7%	6%		6%	7%	
100%–124% (48–59 wk GT1; 24–29 wk GT2/3)	66%	28%		64%	37%		61%	37%	
≥125% (≥60 wk GT1; ≥30 wk GT2/3)	11%	9%		22%	19%		28%	25%	
Erythropoiesis stimulating agent use	34%	24%	<.0001	21%	15%	.0001	21%	14%	.001
Granulocyte colony-stimulating factor use	11%	10%	.01	6%	5%	.14	7%	9%	.09
Multiple treatment courses	3%	6%	<.0001	4%	6%	.002	4%	8%	.0005

NOTE. Totals may not add up to 100% because of rounding.
CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HBV, hepatitis B virus; PTSD, posttraumatic stress disorder; SES, socioeconomic status.

sponders, although average laboratory values for both nonresponders and responders for each genotype were still within the normal range. Nonresponders were also more likely to have higher AST/ALT ratios and a diagnosis of cirrhosis. For all 3 genotype cohorts, nonresponders were older and more likely to have diabetes. In individual genotype cohorts, nonresponders differed from responders with regard to several additional patient characteristics that may have implications for survival. For example, GT1 nonresponders were more likely male, overweight or obese, anemic, and more likely to have diagnoses of coronary artery disease and HTN, compared with responders.

For GT1, 1119 patients died during a median follow-up period of 3.8 years (interquartile range, 2.5–5.2 y) after the definitive posttreatment test result. Similarly for GT2, 220 patients died during a median follow-up period of 3.8 years (interquartile range, 2.6–5.1 y), and for GT3, 196 patients died during a median follow-up period of 3.9 years (interquartile range, 2.6–5.2 y).

In unadjusted analyses, SVR was associated with statistically significantly reduced all-cause mortality for GT1, GT2, and GT3 patients (Figure 1). The cumulative mortality curves for responders and nonresponders diverged early in the follow-up period and the reductions in all-cause mortality among responders appear to be clinically significant. For GT1 and GT2 the 5-year mortality rate for responders was approximately half that for nonresponders (GT1, 6.7% vs 14.4%; $P < .0001$; GT2, 7.3% vs 15.9%; $P < .0001$). For GT3 the 5-year mortality rate for responders was approximately a third of that of nonresponders (8.0% vs 24.4%; $P < .0001$). For all 3 genotypes, patients with SVR had comparable 5-year survival rates (approximately 92%–93%).

A similar pattern of significantly reduced mortality associated with SVR was evident when considering mortality per 100 patient years of follow-up evaluation. For GT1, this rate was 1.4 deaths/100 patient years for responders versus 3.1 deaths/100 patient years for nonresponders ($P < .0001$). The comparable rates for the other genotypes were 1.6 versus 3.2 deaths/100 patient years ($P < .0001$) for GT2, and 1.6 versus 5.1 deaths/100 patient years ($P < .0001$) for GT3.

Table 3 presents the hazard ratios for those patient and treatment characteristics that were statistically significant in the multivariate survival models for at least one genotype. SVR was associated independently with significantly reduced all-cause mortality risk for each genotype. In addition, recent tobacco use, low baseline platelet count, and short treatment duration were associated with an increased risk of death for all 3 genotypes. Other results differed by genotype. For the GT1 cohort, male sex, increasing age, decreasing albumin level, increasing AST level, increasing AST/ALT ratio, decreased creatinine clearance, low sodium level, cirrhosis, diabetes, and remote tobacco use all were associated with increased risk of death. For GT2, HTN also was associated with increased risk of death and decreasing albumin and increased AST/ALT ratio were of borderline significance in predicting increased risk of death. For GT3 patients, predictors of increased risk of death also included increasing age, decreasing albumin level, increased AST/ALT ratio, and diabetes.

The hazard ratios for SVR from the 3 sensitivity analyses of multivariate survival models on different cohorts appear in Table 4. Whether we required SVR patients to have an undetectable HCV RNA test result at 24 weeks or later, excluded patients with a diagnosis of cirrhosis before treatment, or included among the nonresponders those patients who did not have a posttreatment HCV RNA, SVR still was associated independently with significantly reduced all-cause mortality for all 3 genotypes.

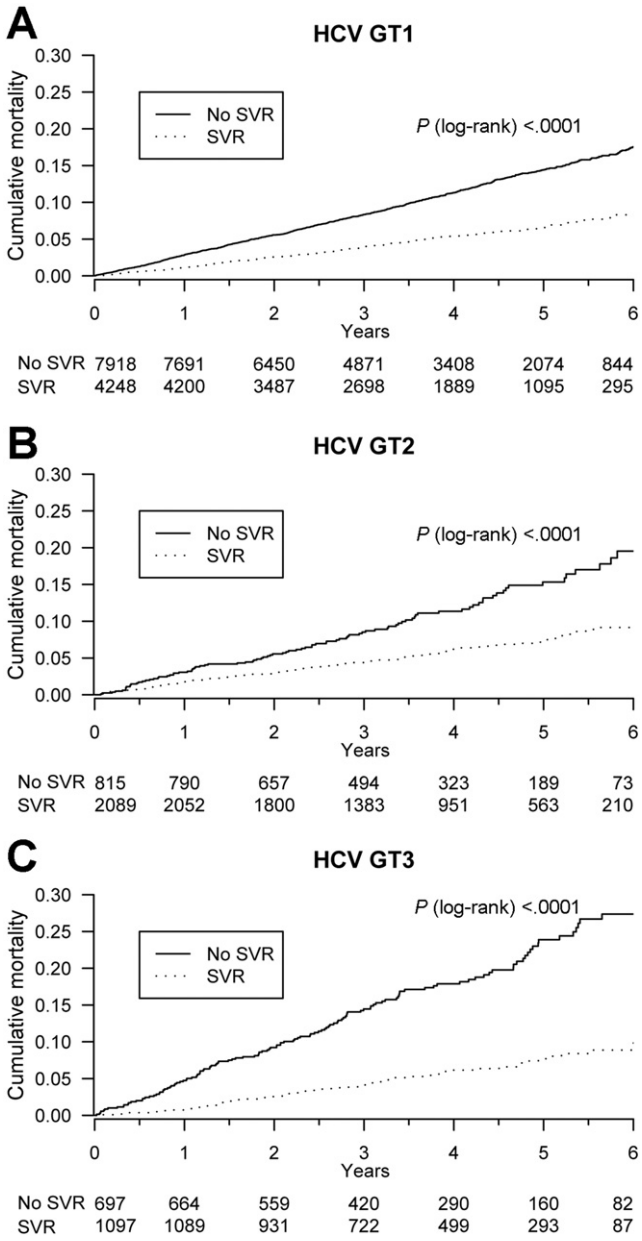

Figure 1. Cumulative mortality for nonresponders (no SVR) and responders (SVR) with number at risk: (*A*) GT1, (*B*) GT2, and (*C*) GT3.

Discussion

In this large US cohort of patients with HCV treated with PEG-IFN/ribavirin in routine medical practice, achieving SVR was associated with a significantly reduced risk of all-cause mortality for patients with GT1, GT2, and GT3, after adjusting for numerous baseline patient characteristics and comorbidities. Previous research has focused on liver-related mortality and thus any potential benefit of SVR on all-cause mortality, particularly in populations with substantial competing risk, has not been clear. Because our cohort was from routine medical practice, the patients had relatively high rates of comorbidities. Despite this, SVR clearly conveyed a substantial reduction in mortality.

The observed reduction in mortality does not appear to be caused by increased liver transplantation in those who had an SVR. Only 210 cohort patients (175 GT1, 14 GT2, and 21 GT3) underwent liver transplantation and only for GT1 were the number of transplant patients sufficient for analysis of SVR rates. GT1 transplant patients were less likely to have SVR regardless of whether we considered patients who underwent transplant after the start, after the end, or at any time in relation to HCV antiviral treatment (data not shown). Thus, the observed difference in mortality is not caused by increased liver transplantation among those with SVR.

The mechanism of the observed reduction in all-cause mortality associated with SVR cannot be elucidated with the present research but is likely multifaceted. Beyond liver-related mechanisms, increasing evidence links chronic infection and chronic inflammatory states with atherosclerotic disease and all-cause mortality.[23,24] Thus, it is plausible (and worthy of additional research) that SVR may reduce chronic inflammation from HCV and thereby contribute to reduced mortality.

Our findings have potential implications for patients, providers, and health care systems that may have been foregoing HCV treatment with PEG-IFN/ribavirin because of the expense and uncertainty about the long-term clinical benefit of that treatment in patients with comorbidities. Despite the presence of relatively high rates of comorbidities, including cirrhosis, chronic obstructive pulmonary disease, coronary artery disease, diabetes, and hypertension, we observed a substantial all-cause mortality benefit with successful HCV treatment of each of the 3 common HCV genotypes. In addition, SVR still was associated with a substantial mortality benefit in patients without an existing diagnosis of cirrhosis who may be considered at reduced mortality risk from their HCV infection.

New HCV treatment regimens, particularly protease inhibitors and/or polymerase inhibitors, promise to increase SVR rates in the near term. Future work will be required to assess the effectiveness of these new agents in routine medical care, but it is reasonable to anticipate that the beneficial effect of SVR we observed in this cohort may accrue to greater numbers of patients assuming widespread availability and use of these new agents.

Finally, our findings serve as a reminder that patients with HCV may have other comorbidities associated with increased mortality that may be amenable to intervention regardless of HCV treatment status. Recent tobacco use was associated with increased risk of death for all 3 genotype. Diabetes was associated with increased mortality risk among GT1 and GT3 patients, and HTN was associated with increased risk among GT2 patients. It is possible that efforts to decrease smoking, improve glycemic control, or improve blood pressure could provide substantial reductions in mortality in the population with chronic HCV regardless of whether they receive antiviral treatment.

This project had limitations, many of which are inherent in observational studies. Because many of our measures of comorbidities rely on ICD-9 coding, it is likely that some diagnoses of interest are underreported, although it is reasonable to assume that the rate of underreporting is similar between responders and nonresponders. Cirrhosis may be additionally underreported because of the ambiguity in noninvasive clinical criteria for the diagnosis. We do not have information about the liver fibrosis stage at the start or end of treatment. The

Table 3. Hazard Ratio for Death After Treatment With PEG-IFN/Ribavirin

	GT1, HR		GT2, HR		GT3, HR	
	(95% CI)	*P* value	(95% CI)	*P* value	(95% CI)	*P* value
Male	2.68 (1.62–4.42)	.0001				
Age (per 10 y)	1.31 (1.16–1.48)	<.0001			1.59 (1.16–2.19)	.004
Albumin (per 1-g/dL decrease)	1.82 (1.57–2.11)	<.0001	1.39 (1.00–1.94)	.05	1.63 (1.10–2.41)	.01
AST 61–90 U/L (ref. ≤30)	1.33 (1.04–1.69)	.02				
AST >90 U/L (ref. ≤30)	1.53 (1.21–1.95)	.0005				
AST/ALT ratio 0.8–0.99 (ref. <0.6)	1.31 (1.06–1.62)	.01				
AST/ALT ratio 1.0–1.19 (ref. <0.6)	1.63 (1.29–2.05)	<.0001	1.79 (1.08–2.98)	.02		
AST/ALT ratio ≥1.2 (ref. <0.6)	1.97 (1.55–2.49)	<.0001			1.86 (1.03–3.34)	.04
Creatinine clearance <60 mL/min (ref. ≥90)	1.93 (1.25–2.98)	.003				
Platelets 100–149 × 10^9/L (ref. ≥150)	1.45 (1.23–1.71)	<.0001				
Platelets <100 × 10^9/L (ref. ≥150)	1.91 (1.55–2.34)	<.0001	2.24 (1.32–3.82)	.003	2.38 (1.48–3.85)	.0004
Sodium <136 meg/L	1.35 (1.13–1.62)	.001				
Cirrhosis	1.32 (1.13–1.55)	.0006				
COPD	1.23 (1.05–1.44)	.01				
Diabetes	1.30 (1.13–1.50)	.0003			1.85 (1.28–2.67)	.001
HTN			1.79 (1.30–2.48)	.0004		
Recent tobacco use (ref. none)	1.29 (1.11–1.51)	.0008	1.76 (1.26–2.48)	.001	1.61 (1.09–2.38)	.02
Remote tobacco use (ref. none)	1.38 (1.17–1.63)	.0001				
Treatment duration <60% recommended (ref. 100%–124%)	1.43 (1.21–1.68)	<.0001	1.62 (1.06–2.42)	.03	1.75 (1.12–2.70)	.01
SVR	0.70 (0.59–0.83)	<.0001	0.64 (0.46–0.88)	.006	0.51 (0.35–0.73)	.0002

NOTE. Models also controlled for bilirubin, body mass index, hepatitis B virus co-infection, HCV RNA, hemoglobin, diagnosis of coronary artery disease, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent diagnosis of alcohol abuse, anxiety disorder, depression, hard drug use, posttraumatic stress disorder, socioeconomic status instability, multiple treatment courses, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, and year of treatment start.
CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ref, reference.

majority of patients did not undergo liver biopsy in the year before treatment and, for those who did, degree of liver fibrosis is not available as a standardized data element in the Clinical Case Registry. We have no information about cause of death so we cannot address what proportion of the reduction in all-cause mortality may have been owing to reduction in liver-related mortality. The VA population is overwhelmingly male and thus the results may not apply to populations with larger proportions of females. Finally, despite controlling for numerous factors, it is possible that responders and nonresponders differ on unmeasured, and possibly nonmeasurable, factors that might account for the observed difference in long-term clinical outcomes. However, it is difficult to envision that residual confounding could account for the quite substantial difference in mortality we observed associated with SVR.

In conclusion, SVR is associated with improved survival among patients with HCV GT1, GT2, and GT3 and with substantial comorbidities in routine medical practice. These findings extend the prior observations that SVR reduced liver-related mortality and show an all-cause mortality reduction for each of 3 common genotypes. Moreover, these findings strongly support an important and clinically significant benefit of HCV antiviral treatment irrespective of the HCV genotype, patient age, and comorbidities.

Table 4. Results of Primary and Secondary Analysis for Hazard Ratio for Death With SVR

	GT1		GT2		GT3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Univariate	0.45 (0.39–0.52)	<.0001	0.50 (0.38–0.65)	<.0001	0.30 (0.22–0.40)	<.0001
Primary analysis	0.70 (0.59–0.83)	<.0001	0.64 (0.46–0.88)	.006	0.51 (0.35–0.73)	.0002
Secondary analysis						
Accepting as SVR only those patients with undetectable HCV RNA at ≥24 wk after the end of treatment	0.71 (0.60–0.86)	.0003	0.62 (0.44–0.87)	.005	0.51 (0.35–0.75)	.0006
Excluding patients with cirrhosis before treatment	0.72 (0.59–0.88)	.001	0.69 (0.48–0.99)	.049	0.40 (0.26–0.64)	.0001
Including patients with no HCV RNA test after the treatment end date who were alive at the treatment end date	0.60 (0.51–0.71)	<.0001	0.58 (0.43–0.78)	.0002	0.45 (0.32–0.62)	<.0001

CI, confidence interval; HR, hazard ratio.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology*, and at doi:10.1016/j.cgh.2011.03.004.

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Reprint requests

Address requests for reprints to: Lisa I. Backus, MD, PhD, 3801 Miranda Avenue Mail code 132, Palo Alto, California 94304. e-mail: lisa.backus@va.gov; fax: (650) 849-0266.

Conflicts of interest

The authors disclose no conflicts.

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Appendix. Baseline Characteristics Before Treatment With PEG-IFN/Ribavirin

	GT1 (n = 12,166)	GT2 (n = 2904)	GT3 (n = 1794)
Patient characteristics			
Male sex	96%	96%	96%
Mean age, *y* (SD)	51.9 (5.7)	53.0 (6.2)	51.0 (5.8)
Race/ethnicity			
African American	23%	6%	3%
Hispanic	6%	6%	6%
Other/multiple/missing	18%	20%	20%
White	53%	68%	71%
Mean albumin level, *g/dL* (SD)	4.0 (0.4)	4.1 (0.4)	4.0 (0.4)
Mean ALT level, *U/mL* (SD)	90.4 (72.2)	95.7 (87.2)	110.9 (82.9)
Mean AST level, *U/mL* (SD)	66.3 (51.0)	64.4 (54.1)	79.3 (55.9)
Mean AST/ALT ratio (SD)	0.8 (0.4)	0.8 (0.3)	0.8 (0.4)
Mean bilirubin level, *mg/dL* (SD)	0.8 (0.5)	0.7 (0.4)	0.8 (0.4)
Mean BMI, kg/m^2 (SD)	29.2 (5.2)	29.3 (5.4)	28.8 (5.2)
Mean creatinine level, *mg/dL* (SD)	1.0 (0.4)	1.0 (0.3)	1.0 (0.2)
Mean creatinine clearance, *mL/min* (SD)	118.3 (33.6)	116.5 (32.7)	120.5 (34.5)
HBV co-infection	1%	1%	1%
Median HCV RNA, $\times 10^6$ *IU/mL* (IQR)	1.0 (0.5–3.5)	1.8 (0.5–5.0)	0.78 (0.3–2.6)
Mean hemoglobin level, *g/dL* (SD)	15.2 (1.4)	15.2 (1.3)	15.2 (1.3)
Mean platelets level, $\times 10^9$*/L* (SD)	207.7 (71.2)	212.3 (69.8)	195.2 (72.8)
Mean sodium level, *mEq/L* (SD)	139.1 (2.8)	138.9 (3.0)	139.2 (2.8)
Comorbidities			
CAD	13%	13%	10%
Cancer	3%	3%	3%
CHF	2%	2%	2%
Cirrhosis	13%	9%	16%
COPD	14%	16%	15%
CVD	1%	1%	1%
Diabetes	21%	17%	16%
HTN	53%	51%	42%
Schizophrenia	8%	7%	7%
Recent diagnoses			
Alcohol abuse	24%	23%	28%
Anxiety disorder	17%	17%	16%
Depression	35%	35%	38%
Hard drug use	12%	11%	14%
PTSD	16%	18%	15%
SES instability	19%	18%	18%
Tobacco use			
None	48%	47%	43%
Recent	33%	36%	41%
Remote	19%	16%	17%
Treatment characteristics			
Percentage of recommended PEG-IFN duration			
<60% (<29 wk GT1; <15 wk GT2/3)	32%	12%	11%
60%–79% (29–38 wk GT1; 15–19 wk GT2/3)	8%	5%	4%
80%–99% (39–47 wk GT1; 20–23 wk GT 2/3)	9%	6%	6%
100%–124% (48–59 wk GT1; 24–29 wk GT 2/3)	41%	56%	52%
≥125% (≥60 wk GT1; ≥30 wk GT 2/3)	9%	21%	27%
Erythropoiesis stimulating agent use	28%	19%	18%
Granulocyte colony-stimulating factor use	10%	6%	8%
Multiple treatment courses	5%	4%	5%

NOTE. Totals may not add up to 100% because of rounding.

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HBV, hepatitis B virus; PTSD, posttraumatic stress disorder; SES, socioeconomic status.