

Original Investigation

The Risk of Long-term Morbidity and Mortality in Patients With Chronic Hepatitis C

Results From an Analysis of Data From a Department of Veterans Affairs Clinical Registry

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IMPORTANCE The impact of viral load suppression, genotype, race, and other factors on the risk of late-stage liver-related events in patients with hepatitis C (HCV) has been assessed previously using data from small observational cohorts or clinical trials. Data from large real-world practice samples are needed to improve risk factor estimates for late-stage liver events and death in HCV.

OBJECTIVE To describe the natural history of HCV in real-world clinical practice.

DESIGN, SETTING, AND PARTICIPANTS Observational cohort study. Patients with a detectable viral load (>25 IU/mL) and a recorded baseline genotype were selected from the Veterans Affairs (VA) HCV clinical registry (CCR), which compiles electronic medical records data from 1999 to present.

EXPOSURES Risk factors included genotype, race, age, sex, and time to achieving an observed undetected viral load.

MAIN OUTCOMES AND MEASURES The primary outcomes were time to death and time to a composite of liver-related clinical events. Secondary outcomes included the components of the composite clinical outcome. Outcomes were measured using a time-to-event format and were analyzed using Cox proportional hazards models.

RESULTS A total of 28 769 of 360 857 unique HCV CCR patients met all study criteria. Only 24.3% of patients received treatment, and 16.4% of treated patients (4.0% of all patients) achieved an undetectable viral load. The unadjusted death rates were 6.8 (95% CI, 6.0-7.7) per 1000 person-years for patients who achieved viral load suppression vs 21.8 (95% CI, 21.5-22.2) deaths per 1000 person-years in patients who did not achieve this goal. Cox model results found that achieving viral suppression reduced risk of the composite clinical end point by 27% (hazard ratio [HR], 0.73 [95% CI, 0.66-0.82]) and the risk of death by 45% (HR, 0.55 [95% CI, 0.47-0.64]). Genotype 2 patients were at significantly lower risk, and genotype 3 patients were at higher risk for all study outcomes relative to genotype 1. Black patients were at lower risk for all liver events than white patients.

CONCLUSION AND RELEVANCE Achieving an undetectable viral load was associated with decreased hepatic morbidity and mortality. It remains to be determined whether newer treatment regimens can offer higher response rates with fewer adverse effects in real-world settings.

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Hepatitis C virus (HCV) affects approximately 130 to 170 million people worldwide,^{1,2} and an estimated 3.2 million people in the United States.³ This US estimate may be low because high-risk groups such as the incarcerated and the homeless were not included in the data. Alternative estimates put the number of US patients with chronic HCV at between 5.2 million and 7 million.⁴

Patients with HCV are at risk of developing liver-related complications such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC).^{1,2,5-7} Using data from the US Department of Veterans Affairs (VA), Butt et al⁸ found that infection with HCV increased the risk of death by 37%.⁸ Hepatitis C is also the leading indication for liver transplant, and the US incidence of HCC is increasing.⁹ Davis et al¹⁰ used a simulation model to project that 13.1% of US patients living with HCV in 2005 will die of liver-related causes by 2030. Rein et al¹¹ extended this projection to 2060, at which time they estimate that 36.8% of the 2005 HCV cohort will have died due to liver causes.

The impact of genotype and demographic factors on the clinical course of HCV may be significant. For example, genotype 1 is thought to be highly correlated with disease progression, although Seeff⁵ casts some doubt on this conclusion. Kallwitz et al¹² found that BMI and Hispanic ethnicity were associated with disease progression, while African Americans had a lower rate of disease progression than white patients.

Sustained viral response (SVR) to treatment is associated with decreased liver-related morbidity and mortality. The REVEAL HCV study¹³ found a significant association between undetectable viral load and liver-related events in Taiwan. Van der Meer et al¹⁴ found that the 36% of patients with advanced hepatic fibrosis who achieved SVR had reduced all-cause mortality and reduced incidence of liver-related events compared with those who did not achieve SVR.¹⁴

To our knowledge, no previous studies have investigated a wide range of the risk factors associated with mortality and morbidity in a large real-world cohort of patients at all levels of disease progression. The objective of the present research is to use HCV RNA data to quantify the impact of viral load suppression on liver-related morbidity and overall mortality using a large cohort of patients with HCV, including those in the early stages of disease progression, while controlling for the impact of genotype, race, age, sex, and other factors.

Methods

Data

The data used in this study were taken from the VA clinical case registry (CCR) system for HCV-infected patients. The VA institutional review board approved the study. Potential patients with HCV were identified by the presence of an HCV-related *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis code or a positive viral load assessment using the hepatitis C antibody test, the hepatitis C RIBA (recombinant immunoblot assay), or the qualitative hepatitis C RNA test. A local CCR coordinator then manually confirmed or rejected the patient for HCV CCR inclusion. After confirmation, all historical data from the patient's electronic medical record (EMR)

Table 1. Patient Characteristics

Characteristic	Patients ^a (n = 128 769)
Treatment data	
Treated	31 284 (24.3)
Untreated	97 485 (75.7)
Achieved undetectable viral load	
Overall (n = 128 769)	5180 (4.0)
While under treatment (n = 31 284)	5141 (16.4)
No treatment (n = 97 485)	39 (0.04)
Male sex	124 980 (97.06)
Age, mean (SD), y	51.8 (6.9)
Postindex data, mean (SD), y	6.1 (3.0)
Race	
White	66 168 (51.39)
Black	40 239 (31.25)
Asian	168 (0.13)
Other	22 194 (17.24)
HCV genotype	
1	102 191 (79.36)
2	15 113 (11.74)
3	9851 (7.65)
Other	1614 (1.25)
Preindex admission, 6 mo	20 938 (16.26)
Diabetes at baseline	15 091 (11.72)
FIB-4 score, mean (SD) (n = 54420)	2.51 (3.08)
FIB-4 score >3.25	10 397 (19.11)

Abbreviation: HCV, hepatitis C virus.

^a Unless otherwise noted, data are reported as number (percentage) of patients.

were pulled and added to the CCR. The VA EMR system was fully implemented in 1999, and the data period for this study covers the entire period over which EMR data were available from all VA regions from 1999 to 2010.¹⁵

An intermediate patient-level analytic database was created consisting of summary variables for each month before and after the patient's CCR enrollment (index date). Summary data were organized as follows:

1. Patient demographic data were recorded (age in months at baseline, sex, race, ethnicity); race and ethnicity data were based on patient self-report.
2. The patient's diagnostic profile was created, consisting of monthly dichotomous variables reflecting the diagnoses recorded each month.
3. Monthly dichotomous variables were created for hospital admissions for any diagnosis and for liver-related diagnoses.
4. Prescription drug data were used to create monthly variables indicating when patients received HCV-related treatment (peginterferon alfa 2a or 2b, interferon alfa 2a or 2b, interferon alfacon-1, boceprevir, or telaprevir). The use of ribavirin alone was not considered to be a drug therapy for HCV.
5. The objective of treatment is to suppress the patient's HCV viral load to undetectable levels. A primary objective of this

research was to document the impact of viral load suppression, accounting for the temporal relationship between achieving an undetectable viral load and event date. To achieve this, we calculated the time to the first undetectable viral load test result as our covariate of interest and defined our primary and secondary outcomes using time-to-event formats. This approach is less stringent than measuring time to SVR, the gold standard for measuring treatment response. Time to SVR is significantly more difficult to calculate, requiring the determination of the time at which the patient maintained consistent viral load suppression for a minimum of 6 months following the termination of treatment.

Sample Selection Criteria

To estimate the risk reduction achieved if patients achieved viral load suppression, all patients were screened for a detectable baseline HCV viral load (>25 IU/mL). Study patients were also screened for a recorded genotype within 6 months of their index date. Longitudinal data were then used to measure time-to-outcome events and estimate the impact of achieving an undetectable viral load and other factors on event risk.

Primary and Secondary Outcomes

Patients infected with HCV are at risk for progressive liver disease and related complications such as cirrhosis, liver failure, HCC, and death.^{1,2,5-7} The primary outcomes specified for this analysis were all-cause mortality and a composite of newly diagnosed cirrhosis (compensated and decompensated), HCC, or a liver-related hospitalization. The time to the composite event was set at the earliest event date for any of the composite events. Because HCV infections commonly go undiagnosed or untreated until complications are observed, sensitivity analysis was conducted in which clinical composite variables were measured using a 1-year postindex washout period during which the clinical events were not counted. The secondary outcomes included the individual elements of the clinical composite analyzed individually.

Monthly dichotomous variables were created for the outcomes of the study based on recorded diagnostic codes (eg, diagnosis of cirrhosis) and selected CPT-4 codes (*Current Procedural Terminology, Fourth Edition*) included in data from hospital admissions and outpatient services. Hospitalizations were defined as being liver related if the primary diagnosis for the hospitalization was one of those listed in the eAppendix in the Supplement, building on the fact that all study patients had a positive HCV viral load. Cirrhosis and HCC outcomes were compiled by searching the inpatient, outpatient, and problem lists for ICD-9 codes 571.5, 571.2, and 571.6; and 155, 155.1, and 155.2, respectively. Decompensated cirrhosis was defined as a diagnosis of cirrhosis and a diagnosis of hepatic coma (70.44, 71.71, 348.3, 348.31, 572.2), portal hypertension (572.3), hepatorenal syndrome (572.4), jaundice (782.4), ascites (789.59), or esophageal varices (456, 456.1, 456.2, 456.21) or a FIB-4 score¹⁶ higher than 3.25. The FIB-4 score can also be segmented into 3 categories that have been found to correctly classify nearly 73% of liver biopsies and to have an 82.1% positive predictive value to confirm the existence of significant fibrosis in an HCV-infected cohort.¹⁶

Statistical Methods

The time-to-event variables for primary and secondary outcomes were analyzed using Cox proportional hazards models to test the correlation between potential predictors and study end points. Time to first observed undetected viral load was included in the analyses as a time-dependent independent variable to measure the impact of viral load suppression on each primary and secondary liver-related event controlling for genotype, race, age, sex, and other factors. Race and ethnicity were initially included as separate categories, but the significant correlation between race and ethnicity in the VA sample resulted in only race being included in the final model specifications. The impact of a diabetes diagnosis at baseline and any hospital admission in the 6 months prior to the patient's index date were included in our list of risk factors based on statistical significance.

A sensitivity analysis was conducted using only those patients with a baseline FIB-4 score to test if the core results on the impact of viral load suppression, genotype, and other factors were sensitive to controlling statistically for the patient's baseline fibrosis level.

Results

Descriptive Statistics

The HCV CCR database contained information on 360 857 unique patients from which a population of 128 769 patients met all study inclusion criteria, including a detectable viral load and genotype data at baseline. Only 24.3% of patients in the analytic sample received treatment at any time following HCV diagnosis, while only 16.4% of treated patients achieved an undetectable viral load after treatment (Table 1). The mean (SD) postindex period was 6.1 (3.0) years. The VA patients with HCV were predominately men of either white or black race (51.4% and 31.3%, respectively). The mean (SD) age was 52.0 (6.9) years, and close to 80% of patients were genotype 1. Just over 42% of study sample patients had baseline data for their fibrosis stage at baseline (FIB-4 score), and only 19% had a FIB-4 score higher than 3.25, which is correlated with a Metavir fibrosis stage of F3 to F4¹⁶ or an Ishak fibrosis stage of F4 to F6.¹⁷ The FIB-4 score was not used in the core analysis owing to this high level of missing data. Instead, a sensitivity analysis was conducted using only those patients with baseline FIB-4 scores, and the patient's FIB-4 category was entered as a potential risk factor.

Absolute Risk of Liver-Related Events and Death

Table 2 lists data on the absolute risk of the composite event and death across the risk factors of interest in this analysis. There were a total of 35 253 composite events and 15 458 deaths in our sample over a total of 734 829 person-years of data. Significantly higher event rates and death rates were experienced by male patients, white patients, and patients with genotype 3. Higher unadjusted composite event rates were found in treated patients than in untreated patients and in those who achieved viral suppression than in those who did not. However, patients who achieved viral suppression exhibited lower unadjusted death rates, which may reflect the delays in therapy until patient became symptomatic.

Table 2. Absolute Event Risk by Risk Group

Risk Group	Event Incidence Rates per 1000 Person-years ^a (95% CI)					
	Cirrhosis	Decomp Cirrhosis	Hospital Admission	HCC	Composite	Death
Sex						
Male	27.7 (27.3-28.1)	12.0 (11.8-12.3)	46.6 (46.0-47.1)	6.4 (6.2-6.6)	62.7 (62.0-63.4)	21.4 (21.0-21.7)
Female	17.8 (16.1-19.7)	5.4 (4.6-6.6)	40.5 (37.7-43.5)	1.4 (1.0-2.0)	52.2 (48.9-55.6)	10.5 (9.3-12.0)
P value	<.001	<.001	.001	<.001	<.001	<.001
Age at diagnosis, y						
<45	16.0 (15.3-16.9)	5.8 (5.3-6.3)	46.9 (45.5-48.4)	1.7 (1.4-1.9)	56.6 (55.0-58.2)	11.4 (10.8-12.1)
45-50	24.4 (23.7-25.1)	9.7 (9.3-10.1)	47.7 (46.7-48.7)	4.0 (3.7-4.3)	61.0 (59.8-62.2)	16.3 (15.8-16.9)
50-55	29.5 (28.8-30.3)	13.2 (12.7-13.6)	46.7 (45.8-47.7)	7.1 (6.8-7.4)	63.4 (62.3-64.5)	21.9 (21.3-22.5)
55-60	34.9 (33.8-36.0)	16.3 (15.5-17.0)	46.2 (44.9-47.5)	9.7 (9.1-10.2)	67.1 (65.5-68.8)	25.9 (25.0-26.8)
60-65	39.0 (36.8-41.4)	17.2 (15.8-18.7)	42.5 (40.2-45.0)	11.8 (10.7-13.1)	67.6 (64.4-70.8)	32.4 (30.5-34.4)
>65	31.9 (29.5-34.5)	14.4 (12.9-16.1)	36.2 (33.6-38.9)	12.8 (11.4-14.4)	57.7 (54.3-61.3)	57.7 (54.7-61.0)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Race						
White	33.8 (33.2-34.4)	15.6 (15.2-16.0)	54.9 (54.0-55.7)	6.9 (6.6-7.2)	73.3 (72.3-74.3)	22.2 (21.7-22.7)
Black	18.9 (18.4-19.5)	6.9 (6.6-7.3)	42.7 (41.8-43.7)	5.3 (5.0-5.6)	55.6 (54.5-56.7)	15.8 (15.3-16.4)
Other	25.4 (24.5-26.3)	10.1 (9.5-10.6)	29.9 (28.9-30.9)	5.9 (5.5-6.3)	45.6 (44.4-46.9)	27.1 (26.2-28.0)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Prior hospital admission						
No prior admission	27.6 (27.2-28.1)	11.3 (11.1-11.6)	39.4 (38.9-40.0)	6.2 (6.0-6.4)	56.6 (56.0-57.3)	19.4 (19.0-19.7)
Prior admission	26.3 (25.3-27.3)	14.3 (13.6-15.0)	89.6 (87.6-91.6)	6.1 (5.7-6.6)	97.8 (95.6-100.0)	29.6 (28.6-30.6)
P value	.07	<.001	.001	.55	<.001	<.001
HCV genotype						
1	27.4 (27.0-27.9)	11.7 (11.4-12.0)	46.8 (46.2-47.4)	6.3 (6.1-6.5)	62.9 (62.2-63.7)	21.0 (20.6-21.4)
2	20.8 (19.8-21.8)	8.1 (7.5-8.7)	38.3 (36.9-39.7)	3.8 (3.4-4.2)	51.6 (49.9-53.3)	19.2 (18.3-20.2)
3	38.9 (37.1-40.7)	19.3 (18.2-20.5)	55.7 (53.6-57.9)	9.6 (8.8-10.5)	76.0 (73.4-78.8)	24.6 (23.3-26.0)
Other	24.3 (21.2-27.9)	10.8 (8.9-13.2)	42.7 (38.4-47.5)	4.8 (3.6-6.4)	56.5 (51.3-62.2)	20.2 (17.5-23.3)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Diabetes at baseline						
Yes	36.1 (34.8-37.5)	15.5 (14.7-16.4)	52.9 (51.3-54.7)	8.7 (8.1-9.4)	73.8 (71.7-76.0)	33.2 (32.0-34.5)
No	26.3 (25.9-26.8)	11.3 (11.1-11.6)	45.5 (45.0-46.1)	5.9 (5.7-6.1)	61.0 (60.3-61.6)	19.5 (19.1-19.8)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Treated						
Yes	36.3 (35.4-37.2)	10.7 (10.3-11.2)	45.0 (44.0-46.0)	5.1 (4.8-5.4)	73.3 (72.0-74.7)	12.0 (11.6-12.5)
No	24.1 (23.6-24.5)	12.3 (12.0-12.6)	46.9 (46.3-47.5)	6.7 (6.4-6.9)	58.3 (57.6-59.1)	24.6 (24.2-25.1)
P value	<.001	<.001	<.001	.19	<.001	<.001
Achieved undetectable VL						
Yes	29.8 (28.0-31.7)	7.3 (6.5-8.2)	40.7 (38.6-43.0)	3.7 (3.2-4.4)	66.2 (63.2-69.2)	6.8 (6.0-7.7)
No	27.3 (26.9-27.7)	12.1 (11.8-12.3)	46.7 (46.1-47.2)	6.4 (6.2-6.5)	62.2 (61.5-62.8)	21.8 (21.5-22.2)
P value	<.001	<.001	<.11	<.001	<.001	<.001
Total events, No. (%)	17 926 (14.5)	8429 (6.6)	28 730 (22.3)	4517 (3.5)	35 253 (28.6)	15 458 (12.0)

Abbreviations: Decomp, decompensated; HCC, hepatocellular carcinoma; VL, viral load.

^a P values are reported for comparisons across categories.

Predictors of Liver-Related Events

The factors associated with our primary outcomes are listed in Table 3.

Viral Load Suppression and Genotype

Patients who achieved an undetectable viral load significantly reduced their risk of the composite clinical end point by 27% (hazard ratio [HR], 0.73 [95% CI, 0.66-0.82]) and their risk of death by 45% (HR, 0.55 [95% CI, 0.47-0.60]) relative to

patients with a detectable viral load over their entire postindex period. The risk reduction associated with the composite clinical end point measured after a 1-year washout period increased slightly to a reduction of 28% (HR, 0.72 [95% CI, 0.64-0.81]).

Patients with genotype 2 were consistently at lower marginal risk for liver-related events compared with patients with the more common genotype 1, controlling for viral load suppression and other risk factors. The risk reduction for the com-

Table 3. Impact of Viral Clearance and Other Risk Factors on the Risk of Late-Stage Liver Events^a

Patient Characteristic	Composite of Clinical Outcomes		
	All Events (n = 123 065)	1-Year Washout (n = 106 947)	Death (n = 128 769)
Events, No. (%)	35 253 (28.6)	18 595 (17.4)	15 458 (12.0)
Male sex	1.11 ^b (1.04-1.19)	1.12 ^b (1.02-1.21)	1.58 ^c (1.38-1.80)
Age	1.003 ^b (1.0028-1.0032)	1.001 ^c (1.0012-1.0016)	1.06 ^b (1.05-1.06)
Race			
White	1 [Reference]	1 [Reference]	1 [Reference]
Black	0.72 ^c (0.71-0.74)	0.76 ^c (0.74-0.79)	0.65 ^c (0.62-0.67)
Other	0.65 ^c (0.63-0.68)	0.61 ^c (0.58-0.63)	1.20 ^c (1.16-1.25)
Prior admission (6 mo)	1.60 ^c (1.56-1.65)	1.55 ^c (1.49-1.60)	1.73 ^c (1.66-1.79)
HCV genotype			
1	1 [Reference]	1 [Reference]	1 [Reference]
2	0.77 ^c (0.74-0.80)	0.77 ^c (0.73-0.80)	0.80 ^c (0.76-0.84)
3	1.11 ^c (1.07-1.16)	1.10 ^b (1.05-1.16)	1.17 ^c (1.11-1.24)
Other	0.89 ^d (0.80-0.98)	0.91 (0.81-1.03)	0.96 (0.83-1.11)
Diabetes at baseline	1.22 ^c (1.18-1.27)	1.25 ^c (1.20-1.30)	1.57 ^c (1.50-1.63)
Achieved undetectable viral load	0.73 ^c (0.66-0.82)	0.72 ^c (0.64-0.81)	0.55 ^c (0.47-0.64)

Abbreviation: HCV, hepatitis C virus.

^a Unless otherwise noted, all data reported as hazard ratio (95% CI); estimates adjusted for the risk factors in the table for which individual results are presented and for the patient's baseline diagnostic profile.

^b *P* < .01.

^c *P* < .001.

^d *P* < .05.

Table 4. Impact of Viral Clearance and Other Risk Factors on the Risk of Secondary Outcomes^a

Patient Characteristic	Cirrhosis (n = 123 988)	Decompensated Cirrhosis (n = 128 055)	Liver-Related Hospitalization (n = 128 769)	Hepatocellular Carcinoma (n = 128 481)
Events, No. (%)	17 926 (14.5%)	8429 (6.6%)	28 730 (22.3%)	4517 (3.5%)
Male sex	1.35 ^b (1.21-1.50)	1.81 ^b (1.50-2.19)	1.09 ^c (1.01-1.17)	3.41 ^b (2.39-4.88)
Age	1.02 ^d (1.02-1.02)	1.04 ^d (1.04-1.049)	0.99 ^d (0.99-0.99)	1.07 ^d (1.07-1.07)
Race				
White	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Black	0.54 ^b (0.52-0.56)	0.42 ^b (0.40-0.45)	0.74 ^b (0.72-0.76)	0.73 ^b (0.68-0.78)
Other	0.73 ^b (0.70-0.76)	0.63 ^b (0.59-0.67)	0.58 ^b (0.56-0.60)	0.80 ^b (0.74-0.87)
Preindex admission (6 mo)	1.02 (0.97-1.06)	1.26 ^b (1.19-1.33)	2.05 ^b (1.99-2.11)	1.07 (0.99-1.17)
HCV genotype				
1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
2	0.64 ^b (0.61-0.68)	0.56 ^b (0.52-0.61)	0.80 ^c (0.76-0.83)	0.52 ^d (0.46-0.58)
3	1.24 ^b (1.18-1.31)	1.42 ^b (1.32-1.52)	1.10 ^b (1.05-1.15)	1.63 ^b (1.47-1.79)
Other	0.87 (0.75-1.00)	0.931 (0.76-1.15)	0.89 ^b (0.79-0.99)	0.77 (0.57-1.04)
Diabetes at baseline	1.38 ^b (1.32-1.44)	1.42 ^b (1.33-1.51)	1.19 ^b (1.15-1.24)	1.31 ^b (1.21-1.42)
Achieved undetectable viral load	0.62 ^b (0.54-0.73)	0.48 ^b (0.38-0.61)	0.71 ^b (0.63-0.80)	0.62 ^d (0.42-0.81)

Abbreviation: HCV, hepatitis C virus.

^a Unless otherwise noted, all data reported as hazard ratio (95% CI); estimates adjusted for the risk factors in the table for which individual results are presented and for the patient's baseline diagnostic profile.

^b *P* < .001

^c *P* < .05.

^d *P* < .01.

posite end point was 23% (HR, 0.77 [95% CI, 0.74-0.80]). The risk of all-cause mortality for genotype 2 patients was reduced by 20% relative to genotype 1 patients (HR, 0.80 [95% CI, 0.76-0.84]). Patients with genotype 3 were consistently at higher risk than patients with genotype 1. The estimates of marginal increased risk for those with genotype 3 ranged between 11% for the composite clinical end point (HR, 1.11 [95% CI, 1.07-1.16]) to a 17% increase in the risk of death (HR, 1.17 [95% CI, 1.11-1.24]). Other genotypes were infrequent in the VA patient population and were collapsed into a single category for which the estimated HRs were not generally significant.

Patient Characteristics

Male sex significantly increased the risk of the composite clinical outcome by 11% (HR, 1.11 [95% CI, 1.04-1.19]) and the risk of death by 58% (HR, 1.58 [95% CI, 1.38-1.80]). Each addi-

tional year of age increased the risk of death by 6% (HR, 1.06 [95% CI, 1.05-1.06]) but only increased the risk of the composite outcome by less than 1% (HR, 1.0001 [95% CI, 1.0012-1.0016]). Whites were consistently at higher risk for all late-stage liver events than blacks and other races. A diagnosis of diabetes at baseline and a hospital admission within 6 months prior to the index date were significantly associated with liver-related events.

Secondary Outcomes

The risk prediction models for the individual late-stage liver events that compose the composite clinical outcome are listed in Table 4. As with the primary outcomes, achieving an undetectable viral load significantly reduced the risk of all clinical events. Other estimates were consistent with the results for the composite event.

Table 5. Impact of Viral Clearance on the Risk of Late-Stage Liver Events Adjusting for Fibrosis Stage^a

Patient Characteristic	Composite of Clinical Outcomes		
	All Events (n = 51 831)	1-Year Washout (n = 46 059)	Death (n = 54 420)
Events, No. (%)	16 291 (31.4)	10 649 (23.1)	7639 (14.0)
Male sex	1.03 (0.93-1.15)	1.06 (0.93-1.20)	1.34 ^b (1.12-1.60)
Age	0.99 ^c (0.98-0.99)	0.99 ^c (0.98-0.99)	1.04 ^c (1.04-1.04)
Race			
White	1 [Reference]	1 [Reference]	1 [Reference]
Black	0.73 ^c (0.70-0.76)	0.76 ^c (0.72-0.79)	0.70 ^c (0.66-0.74)
Other	0.64 ^c (0.61-0.68)	0.61 ^c (0.57-0.65)	1.23 ^c (1.16-1.30)
Prior admission (6 mo)	1.4 ^c (1.37-1.47)	1.40 ^c (1.34-1.46)	1.50 ^c (1.42-1.57)
HCV genotype			
1	1 [Reference]	1 [Reference]	1 [Reference]
2	0.82 ^c (0.77-0.87)	0.79 ^c (0.74-0.85)	0.85 ^c (0.79-0.92)
3	0.97 (0.91-1.04)	0.98 (0.91-1.05)	0.94 (0.86-1.03)
Other	0.87 (0.74-1.02)	0.89 (0.74-1.07)	0.84 (0.68-1.04)
Diabetes at baseline	1.18 ^c (1.12-1.24)	1.21 ^c (1.14-1.28)	1.45 ^c (1.37-1.53)
FIB-4 stage			
Ishak F0-F3 (<1.45)	1 [Reference]	1 [Reference]	1 [Reference]
Ishak inconclusive (1.45 to 3.25)	1.47 ^c (1.42-1.54)	1.50 ^c (1.43-1.57)	1.46 ^c (1.37-1.55)
Ishak F4-F6 (>3.25)	3.44 ^c (3.29-3.61)	3.39 ^c (3.21-3.58)	3.77 ^c (3.55-4.00)
Achieved undetectable viral load	0.74 ^b (0.62-0.87)	0.72 ^b (0.60-0.86)	0.53 ^c (0.42-0.67)

Abbreviation: HCV, hepatitis C virus.

^a Unless otherwise noted, all data reported as hazard ratio (95% CI); estimates adjusted for the risk factors in the table for which individual results are presented and for the patient's baseline diagnostic profile.

^b *P* < .01.

^c *P* < .001.

Sensitivity Analysis: Impact of Fibrosis Stage

Risk models for the composite end point and all-cause mortality were reestimated using only patients with a baseline FIB-4 score (n = 54 420), and FIB-4 stage was entered as a potential risk factor. Several results are noteworthy (Table 5). First, our core estimates of the impact of achieving an undetectable viral load on event risk were very robust (Table 3). If anything, the estimated risk reduction associated with viral load suppression increased when the analysis took into account baseline levels of fibrosis. Second, risk of the composite event and all-cause mortality was monotonically and positively related to the patient's baseline fibrosis level. FIB-4 stage 2 increased risk of the composite event by 47% (HR, 1.47 [95% CI, 1.42-1.54]), while stage 3 HR for the composite event was 3.44 (95% CI, 3.29-3.61). The corresponding HRs for the risk of death were 1.46 (95% CI, 1.37-1.55) for stage 2 and 3.77 (95% CI, 3.55-4.00) for stage 3. In the FIB-4 analyses, each additional year of age was estimated to decrease event risk, but this is likely owing to age appearing in the FIB-4 calculation. Genotype 3 was also associated with lower risk than genotype 1 in the FIB-4 sensitivity analyses, but the estimated HRs were not statistically significant.

Discussion

We found that viral load suppression was associated with decreased risk of liver-related events using data from a large cohort of real-world patients with HCV at various stages of disease progression while controlling for other risk factors, including genotype. This study considered a wide range of liver-related events as study outcome variables and measured these

outcomes and viral load suppression as time-dependent outcomes over as long as 10 years, depending on each patient's availability of data. Finally, the risk factors studied here were derived from EMR data and included both baseline data (sex, race, genotype) and other time-dependent risk factors (BMI, age) that take full advantage of the temporal relationships between events and patient risk factors.

Previous research has clearly documented that patients with an undetectable viral load¹⁸ or who achieve SVR due to treatment are at significantly lower risk of late-stage liver events and death.^{14,19} Our results are consistent with these earlier studies. Patients who achieve an undetectable viral load reduce their risk of death by 45% and reduce their risk of our composite end point of liver-related events by 27% relative to those patients whose viral load was detectable over the entire period following their diagnosis. More importantly, very few patients achieve an undetectable viral load without treatment (39 of 97 485 untreated patients).

While antiviral therapy can lead to viral eradication and reduced event risk, its effectiveness under real-world clinical conditions is limited by adverse effects and other factors. In this study, only 1 in 4 patients with HCV and a detectable viral load were willing to initiate treatment. Once treated, only a fraction of patients achieved the minimum treatment response of a single undetectable viral load test. Our rate of treatment "success" of 16.4% is consistent with that of other studies. For example, Kramer et al¹⁹ documented that the SVR rates achieved using standard antiviral therapy in real-world clinical settings ranged from 14% to 24% for HCV genotype 1 and 37% to 52% for genotypes 2 or 3. In the present study, 16.4% of treated patients achieved viral suppression. The independent role of genotype on the risk of liver-related events has been controversial, mostly

because of limited number of patients with non-genotype 1 infection.^{20,21} Our results are consistent with those of Larsen et al,²² who demonstrated that genotypes 1 and 3 may be associated with greater rates of disease progression than other HCV genotypes. Our results are also consistent with prior observations demonstrating low risk of disease progression in African American patients.^{23,24} Kallwitz et al¹² found that both Hispanics and non-Hispanic whites had a higher risk of cirrhosis than blacks (odds ratios, 1.6 and 2.4, respectively). This study found that incidence rates of HCC were also slightly lower in blacks.

Our sensitivity analysis using baseline FIB-4 scores to define fibrosis stages found these staging variables to be highly predictive of hepatic morbidity and mortality. This supports the expanded use of noninvasive fibrosis staging methods as substitutes for liver biopsy. It is noteworthy that the inclusion of baseline FIB-4 levels into the statistical models eliminated the estimated increase in risk associated with genotype 3 relative to genotype 1. The exact reason for the differential risk effects associated with genotype 3 is unclear but may be related to the higher risk of hepatic steatosis in genotype 3 patients.²⁵⁻²⁷

The use of HCV protease inhibitors is associated with a significant increase in SVR rates relative to standard therapy but also with increases in frequency and severity of adverse effects such as anemia, neutropenia, thrombocytopenia, rash, and gastrointestinal events.²⁸ Early reports suggest non-interferon-based therapies will deliver increased SVR rates while reducing associated substantial adverse effects that limit tolerability.²⁹⁻³³ Clearly, new therapeutic options might offer significant benefits to patients and the health care system if their introduction improves the willingness of patients to initiate therapy and the likelihood that the patient will achieve viral suppression leading to SVR. Natural history data and an understanding of the challenges and expectations from patients are essential to help both providers and patients make informed decisions about when to initiate antiviral therapy and to motivate patient adherence.³⁴

There are several important limitations in our study. First the VA study population differs significantly from the US population, consisting mostly of white and black men. Therefore, results for the risk associated with sex and the catch-all category of "other race" should be viewed with caution. Nevertheless, most US patients with HCV are male,^{3,4} and VA is the largest provider of care to chronically HCV-infected patients in the United States.³⁵

We did not measure SVR, which requires that an undetectable viral load be maintained for 6 months following the termination of treatment. Instead, we used time to the pa-

tient's first undetectable viral load test. It is possible that patients achieving viral load suppression at 1 point can relapse. Nevertheless, our findings are consistent with those of previous studies that even suboptimal therapy is associated with survival benefits.⁸

The sensitivity of HCV viral load tests has changed over time, presented a challenge in defining an "undetectable" viral load. Many older tests used prior to 2004 have a lower threshold of 600 IU/mL, below which the result would be reported as undetectable. Newer tests are sensitive down to 10 IU/mL. For patients with more sensitive tests, we chose to define reported values under 25 IU/mL as undetectable. This overclassification of cases as being undetectable excluded some patients with baseline detectable viral loads from the study sample. Misclassification of some patients as having achieved viral suppression was much less likely because these measurements were made later in the data period. If viral suppression is based on an older laboratory technology, then some "detectable" postindex test findings would be miscategorized as viral suppression. This created a conservative bias in our estimates of the impact of achieving viral suppression because some patients in this category would have viral loads as high as 600 IU/mL and higher risk.

For 2 reasons, this study did not estimate or control for the effects of treatment on clinical end points and death. First, viral suppression without treatment was exceedingly rare, consisting of only 39 patients of 97 485 untreated patients. Second, the parameters with which to determine if a patient completed an adequate course of therapy vary by genotype and other factors, such as allowable duration on breaks in treatment. While developing counts of continuous days of therapy has been used by this research team in the past,³⁶ we elected to use viral load suppression as our measure of treatment success.

Finally, our study did not capture medical care outside the VA system, such as the Medicare program, which may cloud the relationship between viral load suppression and event risk. For example, viral load suppression is highly correlated with expensive treatment that was not well covered in the Medicare program before Part D became effective in 2006. Even when the treatment is covered, drug copayments and the cost of physician visits for injections constitute a significant financial burden. This suggests that treated patients use the VA system, which likely rolls over into treatment for any future liver-related events. If true, this would result in an underestimate of the impact of viral load suppression on event risk. Fortunately, the problem of missing outcome data does not apply to mortality, where viral load suppression has a larger estimated effect.

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