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ORIGINAL ARTICLE

All-Cause Mortality and Liver-Related Outcomes Following Successful Antiviral Treatment for Chronic Hepatitis C

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Abstract
Background Antiviral therapy for the hepatitis C virus (HCV) reduces all-cause and liver-related morbidity and mortality. Few studies are available from populations with multiple medical and psychiatric comorbidities where the impact of successful antiviral therapy might be limited.
Aim The purpose of this study was to determine the effect of sustained virologic response (SVR) on all-cause and liver-related mortality in a cohort of HCV patients treated in an integrated hepatitis/mental health clinic.
Methods This was a retrospective review of all patients who initiated antiviral treatment for chronic HCV between January 1, 1997 and December 31, 2009. Cox regression analysis was used to determine factors involved in all-cause mortality, liver-related events and hepatocellular carcinoma.
Results A total of 536 patients were included in the analysis. Median follow-up was 7.5 years. Liver and non-liver-related mortality occurred in 2.7 and 5.0 % of patients with SVR and in 17.8 and 6.4 % of patients without SVR. In a multivariate analysis, SVR was the only factor associated with reduced all-cause mortality (HR 0.47; 95 % CI 0.26–0.85; $p = 0.012$) and reduced liver-related events (HR 0.23; 95 % CI 0.08–0.66, $p = 0.007$). Having stage 4 liver fibrosis increased all-cause mortality (HR 2.50; 95 % CI 1.23–5.08; $p = 0.011$). Thrombocytopenia at baseline (HR 2.66; 95 % CI 1.22–5.79; $p = 0.014$) and stage 4 liver fibrosis (HR 4.87; 95 % CI 1.62–14.53; $p = 0.005$) increased liver-related events.
Conclusions Despite significant medical and psychiatric comorbidities, SVR markedly reduced liver-related outcomes without a significant change in non-liver-related mortality after a median follow-up of 7.5 years.

Keywords Hepatitis C · Mortality · Liver disease · Interferon · Hepatocellular carcinoma · Antiviral therapy

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Introduction

Infection with the HCV is a major public health problem with over 170 million people worldwide and approximately 3.2 million Americans infected [1, 2]. Approximately 30–50 % of people infected with the HCV progress to cirrhosis and then are at risk for variceal bleeding,

encephalopathy, ascites, bacterial peritonitis, hepatocellular carcinoma (HCC) and death [3]. Recent data indicate that as of 2007, deaths from HCV exceeded those from the human immunodeficiency virus (HIV) in the United States and are expected to climb over the next two decades [4].

Antiviral therapy with pegylated interferon and ribavirin is effective, yielding a sustained virologic response (SVR) in 50–80 % of patients depending primarily on genotype and interferon responsiveness. Recent advances in therapy with direct acting antiviral agents have increased the response rates in genotype 1 patients to 74–76 % [5, 6] and future therapies are even more promising [7, 8]. Although SVR is an important outcome and has been shown to be durable, it is the impact of SVR on mortality and morbidity that is most important.

Prior studies of successful antiviral treatment have focused primarily on liver-related mortality and liver-related events [9]. Most studies of the effect of SVR are from non-US populations and focus on outcomes of patients with advanced fibrosis [9–15]. A recent study of Veterans with HCV by Backus and colleagues showed that those who obtained an SVR had lower all-cause mortality than those without SVR, even when controlling for a variety of factors such as alcohol abuse and cardiovascular disease, but the proportion of deaths related to liver-disease was not known [16]. The authors were unable to determine what proportion of the deaths was due to a reduction in liver-related mortality or if SVR affected other parameters and thereby reduced death. In addition, liver biopsy data was not available; therefore, the impact of SVR at different stages of liver disease is unknown. Few data exist for all-cause mortality and liver-related outcomes for US cohorts, especially those that are older, have significant medical comorbidities, and include patients with all stages of fibrosis. Morgan and colleagues used data from the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) study and showed a significant all-cause mortality and liver-related event benefit from a SVR. The study was from a US population but all subjects had advanced fibrosis and patients with significant comorbidities were excluded from the study [12]. Determining the impact of SVR on all-cause mortality and liver-related events in a diverse population can help inform decisions regarding antiviral therapy from patient and provider perspectives and is essential for calculating cost-benefit analyses.

The Department of Veterans Affairs (VA) has been at the forefront of integrating mental health treatment into medical care settings, including HCV care [17]. We have previously shown that patients seen by a mental health practitioner in an integrated care clinic are more likely to obtain a liver biopsy, be adherent to clinical evaluation and despite significant psychiatric comorbidities have similar antiviral treatment outcomes to those without psychiatric or substance use problems [18]. No studies have investigated the impact of integrated care clinics on mortality in HCV patients with severe psychiatric and substance use comorbidities.

The purpose of this study was to determine the impact of an SVR on all-cause mortality and liver-related morbidity and mortality in patients treated in a clinic that utilized an integrated mental health/hepatitis model of care.

Methods

Data were collected by retrospective chart review of all patients who initiated antiviral treatment for chronic HCV between January 1, 1997 and December 31, 2009 at the Minneapolis Veterans Affairs Health Care System (MVAHCS). The date of treatment initiation determined entrance into the data set and the beginning of follow-up. Data were collected as of May 15, 2012. The following information was obtained:

1. Demographic information
2. Regimen and number of antiviral treatments including interferon-alpha monotherapy, interferon-α-2b and ribavirin, pegylated-interferon α-2b or α-2a and ribavirin or consensus interferon and ribavirin
3. Genotype
4. Platelet count within the 2 years before the first antiviral treatment
5. Liver biopsy results using METAVIR scoring system, if available within 5 years prior to the first antiviral treatment [19]
6. Antiviral treatment outcome
7. Death, documented cause of death and date of death. All deaths were verified by another clinician (E.D.) who was blinded to the antiviral treatment outcome
8. Documented liver transplantation and date it occurred
9. Documented diagnosis of HCC and date of diagnosis
10. Co-morbidities from the problem-list: Heart disease (CHF, CAD, etc.) and cerebrovascular accidents, substance use disorders (opioid/cocaine/methamphetamine/cannabis abuse or dependence), alcohol use disorders, depression, posttraumatic stress disorder (PTSD), psychosis (schizophrenia, schizoaffective disorder or psychosis not otherwise specified) and bipolar disorder, and diabetes
11. Whether patients were seen by the co-located mental health provider in the hepatitis integrated care clinic as evidenced by having at least one visit with the mental health practitioner after the initial hepatitis visit but before antiviral treatment initiation

The integrated care clinic has been previously described by Knott et al. [18]. In brief, the clinic consisted of a

mental health practitioner co-located in the hepatitis clinic, systematic screening for mental health and substance use problems of all new patients, referral based on minimal thresholds from the screens and frequent clinical meetings to discuss patient care between disciplines. The clinic was developed in 1997 and fully implemented in 1999.

All-cause mortality, liver-related events and HCC were the primary outcomes of interest. We combined liver-related deaths and liver transplants into liver-related events as a liver transplant represents a failure of antiviral therapy. The date of liver transplant was used as the end point for the study. HCC resulting in death was included in the liver-related event outcome.

This study was approved by the institutional review board at the MVAHCS.

Statistical Analysis

Cox regression analysis was used to determine factors involved in all-cause mortality and liver-related events (mortality and transplantation). Factors identified by univariate analysis were then used in a Cox regression multivariate analysis to determine independent factors associated with changes in all-cause mortality and liver-related events. In multivariate analyses, liver disease stages 0, 1 and 2 were combined and used as the reference as there were so few deaths in these stages. Furthermore, the unknown group was heterogeneous and thus was not included in the multivariate analysis, as we were interested in the effect of known stage on outcome. Cox regression analysis was used to identify factors associated with HCC. Factors identified by univariate analysis were then used in a Cox regression multivariate analysis to determine independent factors associated with the development of HCC. As there were relatively few patients with HCC we excluded stage from the multivariate analysis. Kaplan–Meier survival analysis was used to determine liver-related events for each stage of liver disease. Chi square analyses were used for categorical outcomes and analysis of variance was used for continuous variables.

Results

Study Population

A total of 545 patients were treated between January 1, 1997 and December 31, 2009. Nine patients received antiviral treatment either after obtaining a liver transplant or after being diagnosed with HCC and were excluded from the analysis. Of the remaining 536 patients, 41.4 % (222/536) achieved an SVR. Mean age at first antiviral treatment was 51.4 years; median age was 51.6 years with a range of 36.2–72.5 years. As expected, most patients (97.8 %, 524/536) were male, Caucasian (80.6 %, 432/536) and had genotype 1 virus (70.0 %, 375/536). A majority (78.7 %) of patients had a liver biopsy before antiviral treatment was initiated. Cardiac disease, diabetes and psychiatric disorders were common. Most patients 364 (67.9 %) were treated with pegylated interferon-alpha and ribavirin and 140 (26.1 %) were treated with interferon-alpha and ribavirin, the rest were treated with either interferon monotherapy 16 (3.0 %) or consensus interferon and ribavirin 16 (3.0 %). A total of 66 (12.3 %) patients were treated twice and 16 (3.0 %) were treated three times over the 13 years covered by the study. Baseline clinical characteristics are shown in Table 1.

Follow up Duration

The median (IQR) follow-up duration was 7.5 (4.9–9.8) years. Follow-up was similar for those with an SVR (7.8 years) compared to those without an SVR (7.3 years). Of patients who were living, 365 (83 %) had a clinic visit within 6 months of the data collection date and 404 (93 %) had a visit within 1 year of the date. During the study period, 27 patients (12.1 %) with an SVR and 96 patients (30.6 %) without an SVR experienced a clinical event, i.e. death, HCC or transplant.

All-Cause Mortality

Nineteen patients (8.6 %) with an SVR and 81 patients (25.8 %) without an SVR died during the follow-up period. In the SVR group 6 deaths (2.7 %) were liver-related, 11 (5.0 %) were non-liver related (7 were due to cancer, 4 cardiovascular) and 2 (0.9 %) were unknown. In patients without an SVR the majority of deaths, 56 (17.8 %), were liver-related, 20 (6.4 %) were non-liver related (seven non-HCC cancer, four suicides, three accidents, four cardiovascular, one sepsis and one renal failure) and 5 (1.6 %) were unknown. The difference in unknown deaths was not significantly different between SVR and non-SVR groups (χ^2 (1) = 0.48, $p = 0.49$). Differences in the number of non-liver related deaths between those with an SVR, 11 patients (5.0 %), and those without an SVR, 20 patients (6.4 %) (χ^2 (1) = 0.88, $p = 0.35$), was not significant.

In univariate analyses, obtaining an SVR, integrated care and depression were associated with a decrease in all-cause mortality. Compared to liver disease stages 0 and 1, stages 2 and 3 conferred no increased risk of death but stage 4 and unknown stage were associated with an increased risk of death. Increased all-cause mortality was also associated with thrombocytopenia (platelets below 150,000/cm^2). Other factors such as alcohol and substance use diagnoses, psychosis or bipolar disorder, number of

Table 1 Baseline characteristics

Characteristic	Overall, $n = 536$	Patients with SVR, $n = 222$	Patients without SVR, $n = 314$	p value
Age at first antiviral treatment, years (SD)	51.4 (5.8)	51.2 (5.5)	51.6 (5.9)	ns
Women, *n* (%)	12 (2.2)	5 (2.3)	7 (2.2)	ns
Race, *n* (%)				
Caucasian	432 (80.6)	193 (86.9)	239 (76.1)	<0.05
African American	53 (10.0)	10 (4.5)	43 (13.7)	<0.05
Hispanic	2 (0.4)	1 (0.5)	1 (0.3)	ns
Asian	2 (0.4)	2 (0.9)	0	ns
Native American	8 (1.5)	3 (1.4)	5 (1.6)	ns
Unknown/other	39 (7.3)	13 (5.9)	26 (8.3)	ns
Genotype, *n* (%)				
1	375 (70.0)	122 (55.0)	253 (80.6)	<0.05
2	80 (14.9)	54 (24.3)	26 (8.3)	<0.05
3	66 (12.3)	37 (16.7)	29 (9.2)	<0.05
4	1 (0.2)	0	1 (0.3)	ns
Unknown	14 (2.6)	9 (4.1)	5 (1.6)	ns
Liver biopsy stage, *n* (%)				
0	14 (2.6)	6 (2.7)	8 (2.5)	ns
1	61 (11.6)	37 (16.7)	24 (7.6)	<0.05
2	117 (21.8)	65 (29.3)	52 (16.6)	<0.05
3	117 (21.8)	46 (20.8)	71 (22.6)	ns
4	113 (21.1)	30 (13.5)	83 (26.4)	<0.05
No biopsy	114 (21.3)	38 (17.1)	76 (24.2)	<0.05
Clinical evidence of cirrhosis, *n* (%)	38 (7.1)	11 (5.0)	27 (8.6)	ns
Platelet count, k/cm^2, mean (SD), $n = 446$	185.5 (74.7)	194.1 (67.2)	179.3 (79.2)	0.039
Number with platelet count <150 k/cm^2 (%)	148 (27.6)	49 (22.1)	99 (31.5)	0.008
Cardiac disease, *n* (%)	50 (9.3)	24 (10.8)	26 (8.3)	ns
Diabetes, *n* (%)	115 (21.5)	37 (16.7)	78 (24.8)	0.023
Substance use disorder, *n* (%)	262 (48.9)	114 (51.4)	148 (47.1)	ns
Alcohol use disorders, *n* (%)	194 (36.2)	87 (39.2)	107 (34.1)	ns
Depression, *n* (%)	254 (47.4)	110 (49.5)	144 (45.9)	ns
PTSD, *n* (%)	108 (20.1)	48 (21.6)	60 (19.1)	ns
Psychosis/bipolar disorder, *n* (%)	46 (8.6)	23 (10.4)	23 (7.3)	ns
Integrated care, *n* (%)	263 (49.1)	124 (55.9)	139 (44.3)	0.008

Clinical evidence of cirrhosis was defined as a chart diagnosis by liver specialists in two separate notes

ns non-significance, *PTSD* posttraumatic stress disorder, SD standard deviation, *SVR* sustained virologic response

Psychosis = problem list diagnoses of schizophrenia, schizoaffective disorder or psychosis not otherwise specified

Integrated care = At least one documented visit by a mental health practitioner co-located in the hepatitis clinic

antiviral treatments, genotype, cardiac disease and age were not significantly associated with changes in all-cause mortality (Table 2).

In a multivariate Cox regression analysis, SVR was the only factor that reduced all-cause mortality. Integrated care approached significance ($p = .055$) as a protective factor. Liver disease stage 4 was associated with an increase in all-cause mortality. Thrombocytopenia and depression were not significantly associated with changes in all-cause mortality (Table 3).

Liver-Related Mortality, Transplantation and HCC

There was significantly greater liver-related mortality in patients without an SVR (17.8 %; 56/314) compared to those with an SVR (2.7 %; 6/222), (χ^2 (1) = 29.11, $p < 0.0001$). Only 2 (0.9 %) patients with a SVR compared to 13 (4.1 %) without a SVR received a liver transplant (χ^2 (1) = 5.02, $p = 0.025$).

Cox proportional hazards regression analysis was used to determine factors associated with liver-related events

Table 2 Unadjusted hazard ratios for all-cause mortality and liver-related events after antiviral therapy

Parameter	All-cause mortality		Liver-related event	
	(95 % CI)	*p* value	(95 % CI)	*p* value
SVR	0.31 (0.19–0.51)	<0.0001	0.16 (0.08–0.32)	<0.0001
Integrated care	0.61 (0.41–0.92)	0.017	0.54 (0.37–0.94)	0.027
Genotype 1 versus 2&3	1.61 (0.96–2.69)	ns	2.63 (1.31–5.30)	0.007
Liver disease				
Stages 0,1	Reference		Reference	
2	1.12 (0.45–2.81)	ns	1.53 (0.30–7.90)	ns
3	1.70 (0.73–4.04)	0.232	3.86 (0.86–17.27)	0.077
4	3.92 (1.73–8.80)	0.001	13.42 (3.21–56.02)	<0.0001
Unknown	2.62 (1.14–6.03)	0.024	8.60 (2.03–36.48)	0.004
Diabetes	1.03 (0.64–1.7)	ns	2.04 (1.27–3.26)	0.003
Thrombocytopenia	2.76 (1.81–4.21)	<0.0001	6.26 (3.60–10.90)	<0.0001
Cardiac	2.07 (0.84–5.09)	ns	0.95 (0.44–2.07)	ns
Age	1.03 (0.99–1.07)	ns	1.05 (1.01–1.09)	0.028
Depression	0.64 (0.43–0.96)	0.03	0.70 (0.44–1.11)	ns
Psychosis or bipolar	1.28 (0.59–2.76)	ns	0.42 (0.13–1.34)	ns
SUD	0.94 (0.64–1.40)	ns	0.91 (0.58–1.43)	ns
Alcohol use disorder	0.82 (0.55–1.22)	ns	0.95 (0.59–1.54)	ns
PTSD	0.94 (0.59–1.50)	ns	0.97 (0.56–1.67)	ns

Liver-related event included liver death, transplant. Thrombocytopenia—platelets below 150,000/cm^2. Measure of age is per year above mean age at antiviral treatment start

Table 3 Adjusted multivariate hazard ratios for all-cause mortality and liver-related events after antiviral therapy

Parameter	All-cause mortality		Liver-related event	
	(95 % CI)	*p* value	(95 % CI)	*p* value
SVR	0.47 (0.26–0.85)	0.012	0.23 (0.08–0.66)	0.007
Integrated care	0.60 (0.36–1.01)	0.055	0.54 (0.28–1.02)	0.058
Genotype 1 versus 2&3			2.38 (0.72–7.93)	0.158
Liver disease				
Stages 0,1 and 2	Reference		Reference	
3	1.58 (0.78–3.18)	0.204	2.23 (0.70–7.09)	0.176
4	2.50 (1.23–5.08)	0.011	4.87 (1.62–14.53)	0.005
Diabetes			0.83 (0.41–1.66)	0.6
Thrombocytopenia	1.68 (0.94–3.03)	0.082	2.66 (1.22–5.79)	0.014
Age			1.02 (0.96–1.07)	0.555
Depression	0.87 (0.52–1.45)	0.59		

Liver-related event included liver death and transplant. Measure of age is per year above mean age at antiviral treatment start. Thrombocytopenia defined as less than 150 K/cm^2

(liver-related mortality or liver transplantation). In univariate analyses, obtaining a SVR and integrated care were associated with a decrease in liver-related events. In contrast, age (per year above mean age at treatment start), having liver disease stage 3, stage 4, unknown stage, diabetes, thrombocytopenia and genotype 1 compared to genotypes 2 and 3 were all associated with increased liver-related events. Other factors such as alcohol use diagnoses, substance use diagnoses, psychosis, number of antiviral treatments and cardiac disease were not significantly associated with changes in liver-related events (Table 2).

In a multivariate Cox regression analysis, SVR significantly reduced liver-related events. Integrated care approached significance ($p = 0.058$) as a protective factor. In contrast, thrombocytopenia and liver disease stage 4 were independently associated with an increased risk of a liver-related event (Table 3). Other factors such as age, diabetes, and genotype 1 were not significantly associated with changes in liver deaths or transplantation.

We repeated the analysis after removing the seven patients whose cause of death was unknown. All HRs were essentially unchanged (data not shown).

The risk of HCC increased with increasing fibrosis on liver biopsy. There were no HCC diagnoses in patients with a baseline stage 0 or 1 liver biopsy. There was 2/117 (1.7 %) HCC diagnoses in patients with baseline stage 2

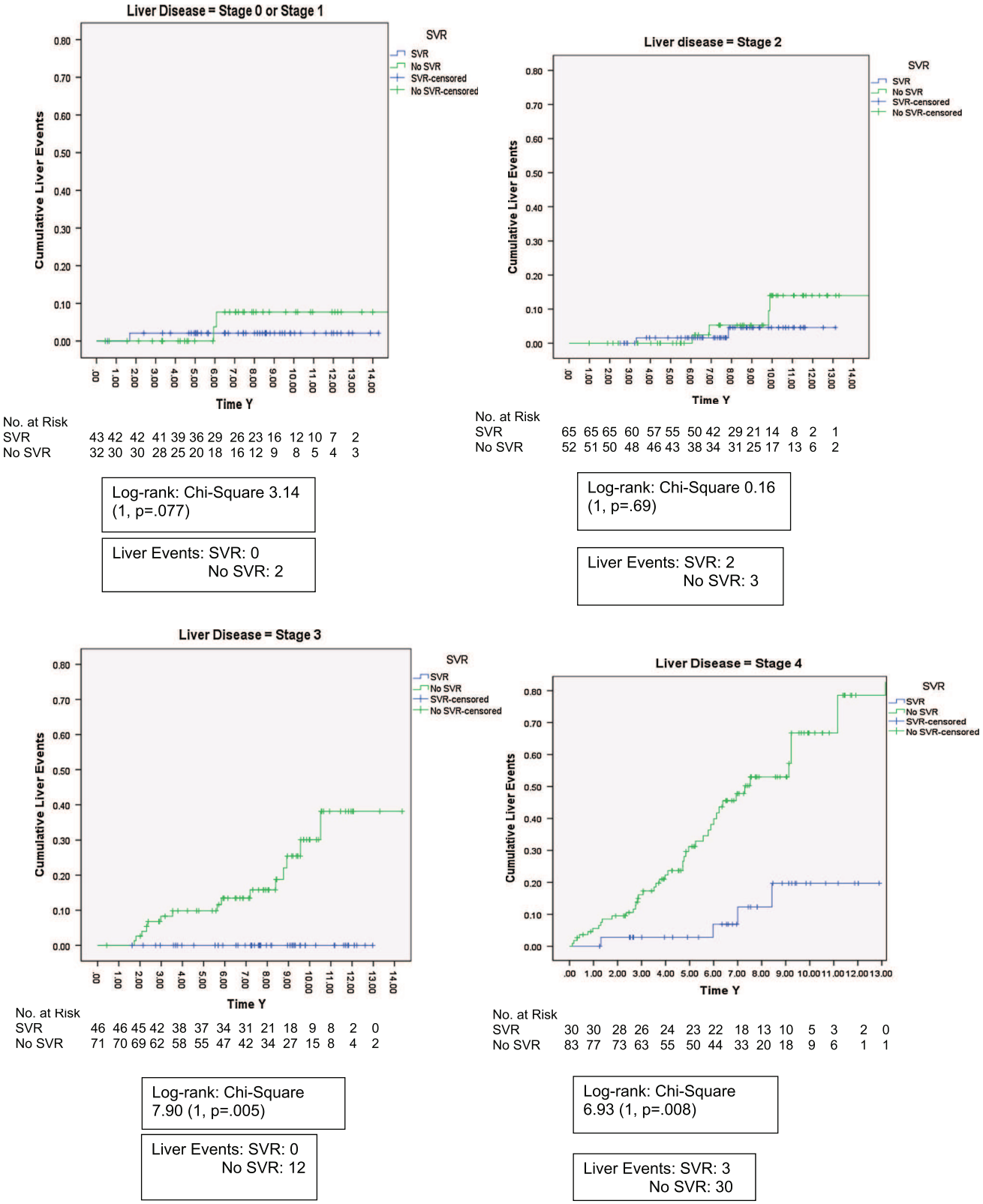

Fig. 1 Cumulative liver-related events for non-responders (no-SVR [sustained virologic response]) and responders (SVR) by liver disease stage at time of initial treatment

liver disease; 12/117 (10.3 %) in stage 3; 17/113 (15.0 %) in stage 4 and 7/114 (6.1 %) in the unknown stage group.

Significantly more patients without an SVR (29; 9.2 %) developed HCC than those with an SVR (9; 4.1 %); (χ^2 (1) = 5.3, $p = 0.021$). Factors associated with an increased risk of HCC in univariate analysis included thrombocytopenia (HR 6.49; 95 % CI 3.10–13.62; $p < 0.0001$), age (per year above mean age at treatment start) (HR 1.07; 95 % CI 1.02–1.13; $p = 0.009$), stage 3 (HR 9.89; 95 % CI 2.21–44.21; $p = .003$), and stage 4 (HR 18.51; 95 % CI 4.27–80.20; $p < 0.0001$). SVR significantly reduced the risk of HCC (HR 0.40; 95 % CI 0.19–0.85; $p = 0.017$). Integrated care, genotype, depression, number of antiviral treatments, alcohol use diagnoses, substance use diagnoses, psychosis or bipolar disorder, diabetes and cardiac disease were not significantly associated with HCC. In multivariate analysis, excluding liver disease stage due to low numbers of patients in each stage, thrombocytopenia (HR 5.32; 95 % CI 2.50–11.31; $p < 0.0001$) was associated with HCC and SVR was protective (HR 0.41; 95 % CI 0.18–0.96; $p = 0.039$).

The impact of SVR on liver-related events for each liver disease stage was also determined by analyzing Kaplan–Meier curves for each stage of liver disease. SVR resulted in fewer liver-related deaths and transplants and reached statistical significance at stages 3 and 4 (Fig. 1).

Discussion

In this large cohort of consecutive patients who received antiviral therapy for chronic HCV and who were followed in an integrated care clinic, SVR was associated with a significant reduction in all-cause mortality and liver-related morbidity and mortality. In addition, SVR was associated with a reduced risk of HCC. Even in this older population who had high rates of medical and psychiatric comorbidities, SVR conferred a nearly twofold reduction in risk of all-cause mortality and a fourfold reduction in liver-related morbidity and mortality. The impact of SVR on all-cause mortality is similar to a prior study in veterans [16] and similar to studies of mortality and liver-related events in non-veterans [13, 20]. Our data confirm the results of Backus et al. [16] and extend their findings by showing that the primary impact of SVR on mortality is through a reduction in liver-related mortality. Since HCV infection is associated with abnormalities of insulin resistance, lipid metabolism and immune function that may improve following SVR, we recognize that studies with longer follow-up after SVR may indicate greater improvements in non-liver-related mortality that are not reflected in the current data [21, 22].

Stage 4 liver disease was the only independent predictor of all-cause mortality in this cohort, increasing the risk of death by more than twofold. Thrombocytopenia conferred an almost threefold increase and stage 4 conferred an almost fivefold increase in liver-related events. This is consistent with a recent study showing increased mortality with lower platelets in patients on a liver transplantation waiting list [23].

Patients in this cohort had significant psychiatric and substance use co-morbidities and were cared for using an integrated care protocol, as described previously [18]. The long-term outcome of these patients is unknown, and they may be expected to have increased mortality based on these comorbidities over time. In univariate analysis we found that being seen by the protocol-based integrated care mental health clinician reduced both all-cause mortality and liver-related events. This may be expected, since prior studies have shown that integrated care can increase eligibility for antiviral treatment and improve treatment outcomes for those with psychiatric and substance use disorders [17, 18, 24]. Given that integrated care was not an independent predictor of liver-related events, in multivariate analyses, one likely explanation for the improved outcome with integrated care is that integrated care was associated with a higher SVR rate. Prior studies have shown that patients who become depressed during antiviral therapy are more likely to stop antiviral treatment [25]. It is possible that patients seen by the mental health clinician were more adherent to antiviral therapy and thus outcome was improved. More data are needed to confirm these findings, but preliminary data from a randomized trial of integrated care indicates increased antiviral treatment rates in patients who receive integrated care [26]. One intriguing finding is the trend towards a reduction in all-cause mortality in those patients seen by the integrated care clinician. This suggests that by integrating care, patients may benefit in non-liver-related ways. Many patients with mental health and substance use disorders often avoid mental health care that is separate from their usual medical care [27]. Integrating mental health care into a medical clinic, as was done in this case, may reduce stigma and enhance effective treatments for mental health and substance use disorders. More work is needed to determine whether the integrated care actually reduces mortality in HCV patients.

One concern raised by the data is the number of suicides and accidents in those patients who did not obtain an SVR. Prior studies suggest that patients with advanced liver disease may be more susceptible to accidents and this may account for the difference in accidents between the two groups [28, 29]. Many practitioners are concerned about the risk of suicidal behavior related to interferon-based treatments but this data suggests that clinicians should also be aware of the potential long-term effect of worsening liver disease on depression and mental functioning. Numerous studies show that chronic illness in general and HCV in particular are highly associated with depression, with most

studies showing rates of depression in the range of 30–40 % [30, 31]. It is possible that by eradicating HCV, patients may have less depression, thus reducing the risk of suicide. The number of patients with an accident or suicide is small and more study is needed to confirm these results.

Not surprisingly mortality and liver-related events increased at each stage of liver fibrosis. In unadjusted analyses stage 3 was associated with a nearly twofold and stage 4 with a nearly fourfold risk of death, and this association was stronger for liver-related events. As shown in the Kaplan–Meier curves, successful antiviral therapy mitigates the risk of liver-related events at all stages and statistically so at stages 3 and 4. The results are consistent with a recent study by van der Meer et al. showing that patients with an SVR with Ishak stages 4, 5 and 6 had reduced all-cause mortality and liver-related events compared to a non-SVR group [13]. Our data further suggest a positive impact of SVR on liver-related events at all liver fibrosis stages. Small absolute differences were apparent between SVR and non-SVR groups and a trend towards improved liver-related events for SVR at stages 0, 1 and 2 were apparent on Kaplan–Meier curves. Differences in mortality may be expected to occur in these groups if they are followed for a longer period of time.

The number of HCC diagnoses increased at each stage of liver disease with 15 % of patients with stage 4 developing HCC. Successful antiviral therapy significantly reduced the risk of developing HCC by greater than twofold. This finding is consistent with prior data [9] and suggests that an SVR is helpful even in patients with advanced liver disease and multiple comorbidities.

There are several limitations to this study including its retrospective nature. Furthermore, as most patients are veterans and male, the results may not apply to other populations. Some patients were lost to follow up and this may have biased the results. However, the status of over 90 % of patients could be verified within 6 months of data collection, validating the data. In addition, we were not able to categorize all deaths which may have impacted the results. However, the effect is likely small as only 7 % of deaths could not be categorized. Although all deaths were verified by a clinician blinded to treatment outcome, bias may still have been introduced particularly in relation to the liver-related cause of death, given the nature of chart review data gathering. However, as the impact of SVR was quite similar between liver-related events and all-cause mortality, the bias was likely small. Given the relatively few HCCs developed in each stage of fibrosis we were not able to determine whether SVR was independently associated with reduced HCC at each stage of liver disease. Finally, although an integrated care protocol was helpful in reducing death; such clinics may not be feasible or widely available in community care settings.

In summary, these data suggest that even in relatively older patients with significant medical and psychiatric comorbidities, SVR reduces all-cause mortality, primarily through a reduction in liver-related events. Patients with cirrhosis had a significantly increased risk of all-cause and liver-related mortality and these patients should be treated aggressively and may need to be monitored more closely. Patients with chronic HCV, even those with significant comorbidities, will benefit from effective antiviral therapy and this effect may be enhanced by integrating mental health and hepatitis care.

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