

Antiviral Therapy Improves Hepatocellular Cancer Survival

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Background: Chronic hepatitis C virus (HCV) infection is a common risk factor for hepatocellular cancer (HCC). Patients with HCV infection are at a higher risk of developing HCC because the virus induces fibrosis in the liver, which may lead to cirrhosis. Early treatment of HCV and achieving a sustained virologic response (SVR) may lead to decreased incidence and mortality associated with HCC.

Methods: We performed a retrospective review of patients at the Memphis Veterans Affairs Medical Center (VAMC) in Tennessee from November 2008 to March 2019 to determine whether treatment of HCV infection makes a difference in overall survival (OS) among patients who develop HCC. Patients were treated with an interferon-based regimen or direct-acting antiviral agents (DAAs). Among the patients with HCV infection who were treated, we identified those who did achieve or did not achieve SVR.

Results: We identified 111 patients with HCV and HCC; 68 were treated for HCV infection. Forty-eight patients received DAA and 20 patients received an interferon-based regimen and 51 achieved SVR. In a multivariate analysis accounting for severity of liver disease, treated patients had

an improved 5-year OS rate, median 1338 days (95% CI, 966-3202) when compared with untreated patients whose median OS was 452 days (95% CI, 242-853) ($P = .0005$). The treatment group had a longer median progression-free survival (PFS) than did the nontreatment group (460 days [95% CI, 294-726] vs 286 days [95% CI, 205-405], $P = .04$). Patients with SVR had an increased 5-year OS compared with patients without SVR (median 1973 days [95% CI, 1222-NA] vs 470 days [95% CI, 242-853], $P < .001$). HCV treatment type (interferon vs DAA) was not found to be associated with either OS or PFS, regardless of time period. Advanced liver disease stage as characterized by a high model for end-stage liver disease (MELD) score (> 10) or high Child-Pugh score (B or C) was associated with worse survival outcome.

Conclusions: A retrospective analysis of patients with HCV infection and HCC confirms that treatment of HCV infection leads to OS benefit among patients with HCC. We further demonstrate that patients with HCV infection who achieve SVR have an OS benefit over patients unable to achieve SVR. The type of treatment, DAA vs an interferon-based regimen, did not show a significant survival benefit.

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Hepatocellular cancer (HCC) is the most common type of hepatic cancers, accounting for 65% of all hepatic cancers.¹

Among all cancers, HCC is one of the fastest growing causes of death in the United States, and the rate of new HCC cases are on the rise over several decades.² There are many risk factors leading to HCC, including alcohol use, obesity, and smoking. Infection with hepatitis C virus (HCV) poses a significant risk.¹

The pathogenesis of HCV-induced carcinogenesis is mediated by a unique host-induced immunologic response. Viral replication induces production of inflammatory factors, such as tumor necrosis factor (TNF- α), interferon (IFN), and oxidative stress on hepatocytes, resulting in cell injury, death, and regeneration. Repetitive cycles of cellular death and regeneration induce fibrosis, which may lead to cirrhosis.³ Hence, early treatment of HCV infection and achieving sustained virologic response (SVR) may lead to decreased incidence and mortality associated with HCC.

Treatment of HCV infection has become more effective with the development of direct-acting antivirals (DAAs) leading to SVR in $> 90\%$ of patients compared with 40 to 50% with IFN-based treatment.^{4,5} DAAs have been proved safe and highly effective in eradicating HCV infection even

in patients with advanced liver disease with decompensated cirrhosis.⁶ Although achieving SVR indicates a complete cure from chronic HCV infection, several studies have shown subsequent risk of developing HCC persists even after successful HCV treatment.⁷⁻⁹ Some studies show that using DAAs to achieve SVR in patients with HCV infection leads to a decreased relative risk of HCC development compared with patients who do not receive treatment.¹⁰⁻¹² But data on HCC risk following DAA-induced SVR vs IFN-induced SVR are somewhat conflicting.

Much of the information regarding the association between SVR and HCC has been gleaned from large data banks without accounting for individual patient characteristics that can be obtained through full chart review. Due to small sample sizes in many chart review studies, the impact that SVR from DAA therapy has on the progression and severity of HCC is not entirely clear. The aim of our study is to evaluate the effect of HCV treatment and SVR status on overall survival (OS) in patients with HCC. Second, we aim to compare survival benefits, if any exist, among the 2 major HCV treatment modalities (IFN vs DAA).

METHODS

We performed a retrospective review of patients at Memphis Veterans Affairs Medical Center

(VAMC) in Tennessee to determine whether treatment for HCV infection in general, and achieving SVR in particular, makes a difference in progression, recurrence, or OS among patients with HCV infection who develop HCC. We identified 111 patients with a diagnosis of both HCV and new or recurrent HCC lesions from November 2008 to March 2019 (Table 1). We divided these patients based on their HCV treatment status, SVR status, and treatment types (IFN vs DAA).

The inclusion criteria were patients aged > 18 years treated at the Memphis VAMC who have HCV infection and developed HCC. Exclusion criteria were patients who developed HCC from other causes such as alcoholic steatohepatitis, hepatitis B virus infection, hemochromatosis, patients without HCV infection, and patients who were not established at the Memphis VAMC. This protocol was approved by the Memphis VAMC Institutional Review Board.

HCC diagnosis was determined using *International Classification of Diseases* codes (9th revision: 155 and 155.2; 10th revision: CD 22 and 22.9). We also used records of multidisciplinary gastrointestinal malignancy tumor conferences to identify patient who had been diagnosed and treated for HCV infection. We identified patients who were treated with DAA vs IFN as well as patients who had achieved SVR (classified as having negative HCV RNA tests at the end of DAA treatment). We were unable to evaluate Barcelona Clinic Liver Cancer staging since this required documented performance status that was not available in many patient records. We selected cases consistent with both treatment for HCV infection and subsequent development of HCC. Patient data included age; OS time; HIV status HCV genotype; time and status of progression to HCC; type and duration of treatment; and alcohol, tobacco, and drug use. Disease status was measured using the Model for End-Stage Liver Disease (MELD) score (Table 2), Milan criteria (Table 3), and Child-Pugh score (Table 4).

Statistical Analysis

OS was measured from the date of HCC diagnosis to the date of death or last follow-up. Progression-free survival (PFS) was defined from the date of HCC treatment initiation to the date of first HCC recurrence. We compared survival data for the SVR and non-SVR subgroups, the HCV treatment vs non-HCV treatment subgroups, and the IFN therapy vs DAA therapy

TABLE 1 Characteristics of Patients With HCV and HCC

Characteristics	Results
Age, mean, y	65.7
< 60 y, No. (%)	22 (20)
> 60 y, No. (%)	89 (80)
Sex, male, No. (%)	111 (100)
Race/ethnicity, No. (%)	
African American	56 (50.5)
White	53 (47.7)
Hispanic	1 (0.9)
Unknown	1 (0.9)
Obesity (body mass index > 30), No. (%)	39 (35.1)
Substance use, No. (%)	
Alcohol	
Current use	73 (65.7)
Never use	11 (9.9)
Former use	27 (24.3)
Tobacco use	
Current use	87 (78.4)
Never use	15 (13.5)
Former use	9 (8.1)
Illicit drug use	
Current use	45 (40.5)
Never use	49 (44.1)
Former use	17 (15.3)
HIV coinfection, No. (%)	2 (1.8)
Liver transplantation, No. (%)	4 (3.6)
Hepatitis treatment, No. (%)	68 (61.3)
Achieved SVR, No. (%)	51 (45.9)
HCV genotype, No. (%)	
1a	56 (50.5)
1b	18 (16.2)
2a	0 (0)
2b	5 (4.5)
3a	1 (0.9)
3b	0 (0)
Unknown	31 (27.9)
MELD score, No. (%)	
< 10	43 (38.7)
10-15	43 (38.7)
> 15	20 (18.0)
Child-Pugh class, No. (%)	
A	79 (71.2)
B	21 (18.9)
C	9 (8.1)
Unknown	2 (1.8)

Abbreviations: HCC, hepatocellular cancer; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; SVR, sustained virologic response.

subgroups, using the Kaplan-Meier method. The differences between subgroups were assessed using a log-rank test. Multivariate analysis using Cox proportional hazards regression model was used to identify factors that had significant impact on OS. Those factors included age; race; alcohol, tobacco, and illicit drug use; SVR status; HCV treatment status; IFN-based regimen vs DAA; MELD, and Child-Pugh scores. The

TABLE 2 Model for End-Stage Liver Disease Scores^{24,a}

Scores	90-Day Mortality, %
≥ 40	71.3
30 - 39	52.6
20 - 29	19.6
10 - 19	6
≤ 9	1.9

^aScore calculated using the formula $9.57 \times \log_e(\text{creatinine}) + 3.78 \times \log_e(\text{total bilirubin}) + 11.2 \times \log_e(\text{international normalized ratio}) + 6.43$.

TABLE 3 Milan Criteria^a

- Single tumor ≤ 5 cm or 3 lesions ≤ 3 cm each
- No evidence of vascular invasion
- No evidence of extrahepatic metastatic disease

^aAll criteria must be met.

TABLE 4 Child-Pugh Classification for Severity of Cirrhosis

Clinical Criteria	Points
Encephalopathy	
None	1
Mild to moderate (grade 1 or 2)	2
Severe (grade 3 or 4)	3
Ascites	
None	1
Mild to moderate (diuretic response)	2
Severe (diuretic refractory)	3
Bilirubin, mg/dL	
< 2	1
2-3	2
> 3	3
Albumin, g/dL	
> 3.5	1
2.8-3.5	2
< 2.8	3
Prothrombin time	
Prolonged, sec	
< 4	1
4-6	2
> 6	3
International normalized ratio	
< 1.7	1
1.7-2.3	2
> 2.3	3
Class scoring (severity)	
A: 5-6 points (least)	
B: 7-9 points (moderate)	
C: 10-15 points (highest)	

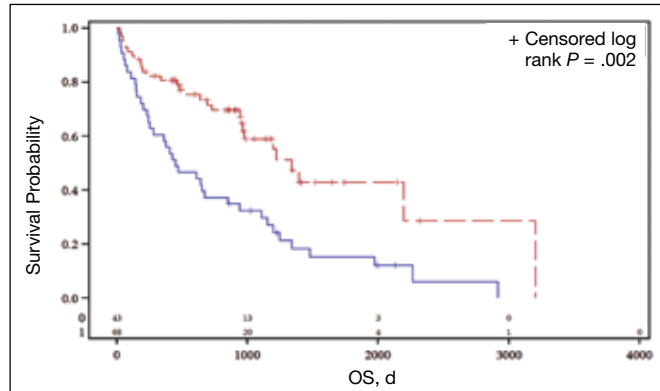
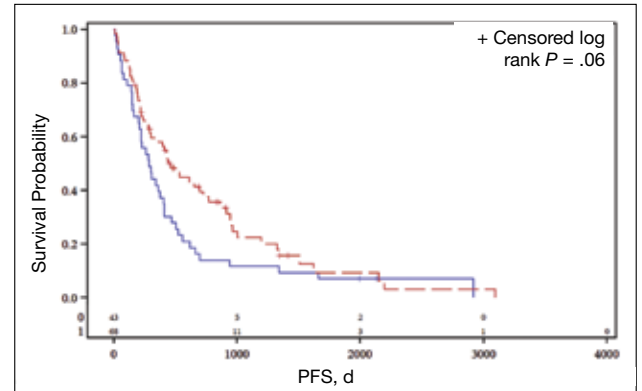
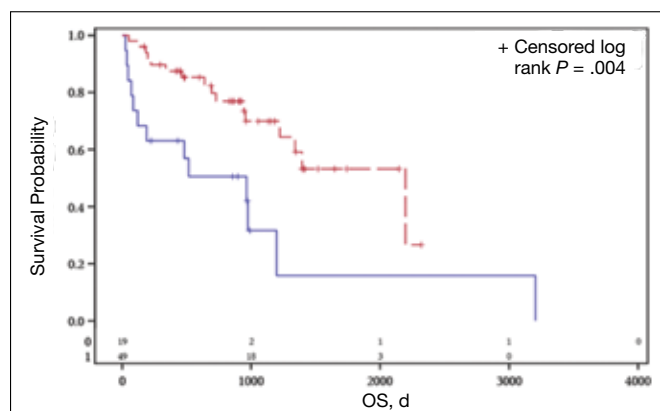
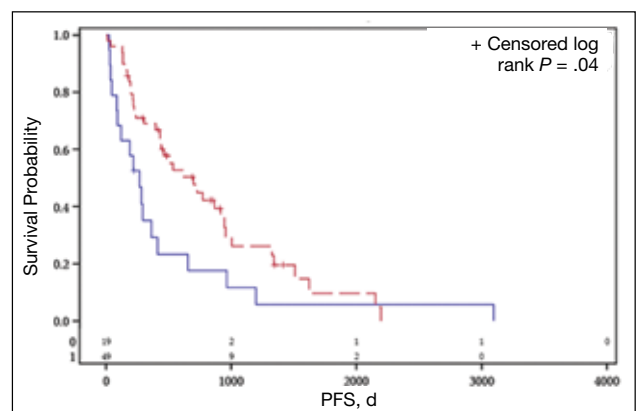
results were expressed as hazard ratios (HRs) and 95% CI. Calculations were made using Statistical Analysis SAS and IBM SPSS software.

RESULTS

The study included 111 patients. The mean age was 65.7 years; all were male and half of were Black patients. The gender imbalance was due to the predominantly male patient population at Memphis VAMC. Among 111 patients with HCV infection and HCC, 68 patients were treated for HCV infection and had significantly improved OS and PFS compared with the nontreatment group. The median 5-year OS was 44.6 months (95% CI, 966-3202) in the treated HCV infection group compared with 15.1 months in the untreated HCV infection group with a Wilcoxon $P = .0005$ (Figure 1). Similarly, patients treated for HCV infection had a significantly better 5-year PFS of 15.3 months (95% CI, 294-726) compared with the nontreatment group 9.5 months (95% CI, 205-405) with a Wilcoxon $P = .04$ (Figure 2).

Among 68 patients treated for HCV infection, 51 achieved SVR, and 34 achieved SVR after the diagnosis of HCC. Patients who achieved SVR had an improved 5-year OS when compared with patients who did not achieve SVR (median 65.8 months [95% CI, 1222-NA] vs 15.7 months [95% CI, 242-853], Wilcoxon $P < .001$) (Figure 3). Similarly, patients with SVR had improved 5-year PFS when compared with the non-SVR group (median 20.5 months [95% CI, 431-914] vs 8.9 months [95% CI, 191-340], Wilcoxon $P = .007$) (Figure 4). Achievement of SVR after HCC diagnosis suggests a significantly improved OS (HR 0.37) compared with achievement prior to HCC diagnosis (HR, 0.65; 95% CI, 0.23-1.82, $P = .41$)

Multivariate Cox regression was used to determine factors with significant survival impact. Advanced age at diagnosis (aged ≥ 65 years) (HR, 0.53; 95% CI, 0.320-0.880; $P = .01$), SVR status (HR, 0.33; 95% CI, 0.190-0.587; $P < .001$), achieving SVR after HCC diagnosis (HR, 0.37; 95% CI, 0.20-0.71; $P = .002$), low MELD score (< 10) (HR, 0.49; 95% CI, 0.30-0.80; $P = .004$) and low Child-Pugh score (class A) (HR, 0.39; 95% CI, 0.24-0.64; $P = .001$) have a significant positive impact on OS. Survival was not significantly influenced by race, tobacco, drug use, HIV or cirrhosis status, or HCV treatment type. In addition, higher Child-Pugh class (B or C), higher MELD score (> 10), and younger age at

FIGURE 1 HCV Treated vs Not-Treated 5-Year OS**FIGURE 2** HCV Treated vs Not-Treated 5-Year PFS**FIGURE 3** SVR vs No SVR 5-Year OS**FIGURE 4** SVR vs No SVR 5-Year PFS

Abbreviations: Abbreviations: HCV, hepatitis C virus; OS, overall survival; PFS, progression-free survival; SVR, sustained virologic response.

diagnosis (< 65 years) have a negative impact on survival outcome (Table 5).

DISCUSSION

The survival benefit of HCV eradication and achieving SVR status has been well established in patients with HCC.¹³ In a retrospective cohort study of 250 patients with HCV infection who had received curative treatment for HCC, multivariate analysis demonstrated that achieving SVR is an independent predictor of OS.¹⁴ The 3-year and 5-year OS rates were 97% and 94% for the SVR group, and 91% and 60% for the non-SVR group, respectively ($P < .001$). Similarly, according to Sou and colleagues, of 122 patients with HCV-related HCC, patients with SVR had longer OS than patients with no SVR ($P = .04$).¹⁵ One of the hypotheses that could explain the survival benefit in patients who achieved SVR is the effect of achieving SVR in reducing persistent liver inflammation and associated liver mortality, and therefore lowering risks of complication in patients with HCC.¹⁶ In our study, multivariate analysis shows

that achieving SVR is associated with significant improved OS (HR, 0.33). In contrast, patients with HCC who have not achieved SVR are associated with worse survival (HR, 3.24). This finding supports early treatment of HCV to obtain SVR in HCV-related patients with HCC, even after development of HCC.

Among 68 patients treated for HCV infection, 45 patients were treated after HCC diagnosis, and 34 patients achieved SVR after HCC diagnosis. The average time between HCV infection treatment after HCC diagnosis was 6 months. Our data suggested that achievement of SVR after HCC diagnosis suggests an improved OS (HR, 0.37) compared with achievement prior to HCC diagnosis (HR, 0.65; 95% CI, 0.23-1.82; $P = .41$). This lack of statistical significance is likely due to small sample size of patients achieving SVR prior to HCC diagnosis. Our results are consistent with the findings regarding the efficacy and timing of DAA treatment in patients with active HCC. According to Singal and colleagues, achieving SVR after DAA therapy may result in improved liver

TABLE 5 Multivariate Survival Analysis

Variables	Hazard Ratio (95% CI)	P value
Age, y		
≥ 65	0.53 (0.32-0.88)	.01
< 65	1.89 (1.14-3.13)	.01
Race		
African American	1.39 (0.85-2.28)	.19
White	1.44 (0.19-10.73)	.72
Substance use		
Alcohol	1.66 (0.91-3.00)	.10
Tobacco	1.54 (0.66-3.61)	.32
Illicit drug	1.17 (0.66-2.07)	.60
Comorbid conditions		
HIV	0.62 (0.08-4.69)	.64
Liver cirrhosis	2.25 (0.95-5.31)	.07
Sustained virologic response		
Yes	0.33 (0.19-0.59)	< .001
No	3.24 (1.85-5.69)	< .001
Before HCC diagnosis	0.65 (0.23-1.82)	.41
After HCC diagnosis	0.37 (0.20-0.71)	.002
Treatment types		
Direct-acting antiviral	0.61 (0.30-1.26)	.18
Interferon-based regimen	1.01 (0.22-4.69)	.11
Model for End-Stage Liver Disease score		
≤ 10	0.49 (0.30-0.80)	.004
> 10	2.202 (1.36-3.58)	.001
Child-Pugh class		
A	0.39 (0.24-0.64)	.001
B or C	2.57 (1.56-4.21)	.001

Abbreviation: HCC, hepatocellular carcinoma.

function and facilitate additional HCC-directed therapy, which potentially improves survival.¹⁷⁻¹⁹

Nagaoki and colleagues found that there was no significant difference in OS in patients with HCC between the DAA and IFN groups. According to the study, the 3-year and 5-year OS rates were 96% and 96% for DAA patients and 93% and 73% for IFN patients, respectively ($P = .16$).¹⁴ This finding is consistent with the results of our study. HCV treatment type (IFN vs DAA) was not found to be associated with either OS or PFS time, regardless of time period.

A higher MELD score (> 10) and a higher Child-Pugh class (B or C) score are associated with worse survival outcome regardless of SVR status. While patients with a low MELD score (≤ 10) have a better survival rate (HR 0.49), a higher MELD score has a significantly higher HR and therefore worse survival outcomes (HR, 2.20). Similarly, patients with Child-Pugh A (HR, 0.39) have a better survival outcome compared with those patients with Child-Pugh class B or C (HR, 2.57). This finding is consistent with re-

sults of multiple studies indicating that advanced liver disease, as measured by a high MELD score and Child-Pugh class score, can be used to predict the survival outcome in patients with HCV-related HCC.²⁰⁻²²

Unlike other studies that look at a single prognostic variable, our study evaluated prognostic impacts of multiple variables (age, SVR status, the order of SVR in relation to HCC development, HCV treatment type, MELD score and Child-Pugh class) in patients with HCC. The study included patients treated for HCV after development of HCC along with other multiple variables leading to OS benefit. It is one of the only studies in the United States that compared 5-year OS and PFS among patients with HCC treated for HCV and achieved SVR. The studies by Nagaoki and colleagues and Sou and colleagues were conducted in Japan, and some of their subset analyses were univariate. Among our study population of veterans, 50% were African American patients, suggesting that they may have similar OS benefit when compared to White patients with HCC and HCV treatment.

Limitations

Our findings were limited in that our study population is too small to conduct further subset analysis that would allow statistical significance of those subsets, such as the suggested benefit of SVR in patients who presented with HCC after antiviral therapy. Another limitation is the all-male population, likely a result of the older veteran population at the Memphis VAMC. The mean age at diagnosis was 65 years, which is slightly higher than the general population. Compared to the SEER database, HCC is most frequently diagnosed among people aged 55 to 64 years.²³ The age difference was likely due to our aging veteran population.

Further studies are needed to determine the significance of SVR on HCC recurrence and treatment. Immunotherapy is now first-line treatment for patients with local advanced HCC. All the immunotherapy studies excluded patients with active HCV infection. Hence, we need more data on HCV treatment timing among patients scheduled to start treatment with immunotherapy.

CONCLUSIONS

In a population of older veterans, treatment of HCV infection leads to OS benefit among patients with HCC. In addition, patients with HCV infection who achieve SVR have an OS

benefit over patients unable to achieve SVR. The type of treatment, DAA vs IFN-based regimen, did not show significant survival benefit.

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