The long-term prognosis in terms of risk or predictors of developing hepatocellular carcinoma (HCC) among patients with sustained virological response (SVR) remains unclear. We conducted a retrospective cohort study using data from the Veterans Affairs VA hepatitis C virus (HCV) Clinical Case Registry in patients with positive HCV RNA between October 1999 and August 2009 and follow-up through December 2010. HCV treatment (interferon with or without ribavirin) and SVR (RNA test negative at least 12 weeks after the end of treatment) were determined. We used Cox's proportional hazards models to calculate hazard ratios (HRs) for potential predictors (demographic, virological, and clinical) associated with HCC development post-SVR. We identified 33,005 HCV-infected individuals who received treatment, of whom 10,817 achieved SVR. Among these patients, 100 developed new HCC during a total follow-up of 30,562 person-years for an overall incidence rate of 0.33% per year. Annual risk of HCC remained considerably high among patients with cirrhosis (1.39%) and those cured after age 64 (0.95%). Patients with diabetes (adjusted HR = 1.88; 1.21-2.91) or genotype 3 infection (adjusted HR = 1.62; 0.96-2.734) were significantly more likely to develop HCC.

Conclusions: Risk of HCC after HCV cure, though considerably reduced, remains relatively high at 0.33% per year. Older age and/or presence of cirrhosis at the time of SVR are associated with a high enough risk to warrant surveillance. Diabetes is also a risk factor for post-SVR HCC. (HEPATOLOGY 2016;64:130-137)
from single centers in Japan, have indicated that cured CHC patients have a significant reduction in their risk of developing HCC compared to untreated or treated, but not cured, controls. However, given the low cure rate coupled with low treatment rate with IFN-based therapies, few studies could assemble a large enough number of cured patients and present long-term follow-up to allow meaningful conclusions about relatively rare outcomes, such as HCC, or examine the determinants of these outcomes.

The required clinical follow up for patients who achieve sustained virological response (SVR) are unclear. For example, HCC surveillance is recommended in most clinical practice guidelines in high-risk groups that are defined based on >1.0% annual risk of developing HCC. However, the available information does not allow for precise estimation of HCC risk or the temporal change of that risk. Furthermore, apart from presence of cirrhosis at or before SVR, there have been no consistently identified risk factors for HCC post-SVR. This information has become important for clinical practice as well as for setting a clinical research agenda in an era of increasingly cured HCV.

We therefore conducted a retrospective cohort study among 10,738 CHC patients with SVR during 1999-2009 to estimate risk of HCC and examine potential determinants of this risk.

Patients and Methods

DATA SOURCES

This study was approved by Baylor College of Medicine’s Institutional Review Board (Houston, TX), and all procedures conformed to the ethical guidelines of the 1975 Declaration of Helsinki. We used data from the Veterans Health Administration (VHA) HCV Clinical Case Registry (CCR), which contains health information for all known HCV-infected patients from 128 VHA facilities nationwide. Data elements in the CCR include date of birth, laboratory test results, outpatient and inpatient VHA pharmacy data, and inpatient and outpatient diagnoses and procedure codes. The Veterans Affairs (VA) Vital Status file, which captures death and corresponding date with up to 97.6% agreement with the National Death Index, was used to ascertain date of death.

STUDY POPULATION

The study cohort included patients with CHC, defined as a positive test for HCV RNA in plasma by qualitative or quantitative assays or genotype test between October 1, 1999, and December 31, 2009. We included patients who received IFN or pegylated IFN (Peg-IFN) therapy (with and without ribavirin [RBV]) and achieved an SVR. We defined SVR as last HCV-RNA test being negative at least 12 weeks after treatment completion as described. We defined the date of earliest indication of SVR (first negative RNA test date of the terminal sequence of negative RNA tests) as the index date for this analysis. We also evaluated HCC incidence in a group of patients who received treatment but had no SVR (last HCV-RNA test after treatment end date was positive) using the last date of treatment as their index date. The non-SVR group was not included in any other analysis.

STUDY EXPOSURE AND OUTCOMES

The primary outcome of the study was new (incident) cases of HCC (International Classification of Disease, Ninth Revision [ICD-9] code 155.0) that was first recorded after the index date. Patients with HCC recorded any time before the index date (prevalent
cases) were excluded to ensure that HCC was newly diagnosed post-treatment. The ICD-9 code-based definition for HCC was validated in a previous study against detailed medical record reviews and shown to have a high positive predictive value. Study follow-up ended at the time of HCC, patient’s death, last visit in the VHA, or January 1, 2010.

**POTENTIAL RISK FACTORS FOR HCC**

We ascertained several baseline risk factors that may be associated with an accelerated or decreased progression to HCC in patients with SVR: age (<45, 45-54, 55-64, and 65+); race (African American, non-Hispanic white, Hispanic, other, or unknown); sex, HCV genotype, cirrhosis, diabetes, alcohol use, human immunodeficiency virus (HIV) infection, hepatitis B virus (HBV) infection, and body mass index (BMI). We identified HIV, diabetes, and alcohol use by the presence of outpatient or inpatient ICD-9 diagnosis codes recorded any time preceding the SVR index date. We defined cirrhosis as the presence of cirrhosis ICD-9 codes (571.2, 571.5, and 571.6); we also examined alternate definitions using an aspartate aminotransferase/platelets ratio index (APRI) >2 any time before the SVR index date and analyzed three definitions of cirrhosis: codes only, APRI >1.77, and APRI >2.0. We defined patients with HBV coinfection as subjects with a positive HBV surface antigen test during the study period. BMI was defined using the height and weight closest to (and before) the SVR index date. Diabetes was examined as a time-dependent exposure variable by continually updating it throughout the study period until event or censor time.

**STATISTICAL ANALYSIS**

We calculated the annualized incidence rates of HCC by dividing the number of incident cases by a denominator of patient-years (PY) follow-up and compared these rates among patients who received antiviral treatment based on SVR and no SVR status. We first examined the incidence rate of HCC overall in patients who were treated with and without SVR.

The remainder of the analyses was limited to the SVR cohort. We estimated the annualized HCC incidence in several subgroups defined by demographic and clinical characteristics in patients with SVR. We generated cumulative hazard function curves, using the Fine-Gray adaptation of Kaplan-Meier’s estimation method to illustrate and compare cumulative incidence of HCC (with death as a competing risk) overall and stratified by several variables of interest (age, cirrhosis, and diabetes) starting at SVR date till the end of the follow-up period. We used the log-rank test to evaluate the differences among these rates by risk factor (cirrhosis, age at time of SVR). We then constructed Cox’s proportional hazards models to examine the association between risk factors and time to development of HCC. Variables with a univariate \( P \text{ value} < 0.20 \) were considered candidate variables for the model, and all variables with a \( P \text{ value} < 0.10 \) were retained in the final model.

We conducted secondary analyses excluding HCC cases that developed during the first year of follow-up; these cases may have been prevalent cases and or have a different biology and risk factors than those that develop subsequently. We also conducted an analysis restricted to patients without significant risk factors to potentially identify patients at very low HCC risk who can be excluded from HCC surveillance programs.

The results of these regressions were expressed as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). No significant departures from proportional hazards were found for the included predictors.

**Results**

**STUDY COHORT**

There were 258,292 patients with a positive HCV-RNA test identified from the HCV CCR; of these, 33,005 received IFN/Peg-IFN with or without RBV. SVR could be determined in 22,197 patients, of whom 10,817 had a documented negative RNA test more than 12 weeks after treatment end date and 11,380 in whom SVR was not achieved (Fig. 1). We subsequently excluded 79 patients in whom HCC was diagnosed on or before the SVR date, resulting in 10,738 patients in the SVR cohort, and excluded 90 patients in whom HCC was diagnosed on or before the treatment end date, resulting in 11,290 in the no SVR cohort (Fig. 1).

**HCC INCIDENCE IN TREATED COHORTS WITH AND WITHOUT SVR**

There were 100 incident cases of HCC diagnosed during 30,562 PY of follow-up after SVR (mean
duration of follow up post-SVR was 2.8 years (SD, 2.0); this yielded an annual HCC incidence rate of 3.27 per 1,000 PY (or 0.327%). This rate was considerably and significantly lower than the 1.32 per 100 PY incidence rate in the group of patients with no SVR (425 HCC cases during 45,509.9 PY follow-up in 11,290 patients treated with no SVR); unadjusted HR of 0.49 (95% CI, 0.46-0.53) for SVR versus non-SVR.

We hand-reviewed a convenience sample of 22 cases of the 100 HCCs among patients with SVR and confirmed HCC diagnosis in 21 of these cases (i.e., positive predictive value [PPV] for ICD-9 codes of 95%). Of these cases, 12 had both cirrhosis diagnosis and high APRI, 6 had high APRI but no cirrhosis diagnosis, and 3 had no cirrhosis diagnosis and no high APRI.

**HCC INCIDENCE AND RISK FACTORS IN PATIENTS WITH SVR**

Table 1 presents the demographic and clinical characteristics of the SVR cohort as well as the annual HCC incidence rate and unadjusted HR for subgroups of patients with each characteristic. Mean age of the SVR cohort was 53.1 years (SD = 6.3) and consisted of mostly male patients (95.3%) of white race (64.4%).

Most were infected with HCV genotype 1 (53.6%) before achieving SVR.

Among patients with SVR who developed HCC, median age at time of HCC diagnosis was 58.0 with interquartile range (IQR) 55.0-61.5. Time from SVR to HCC ranged from 0.04 to 7.33 years, with a median of 1.66 (IQR, 0.61-3.19). Patients with cirrhosis diagnostic codes had the highest annual incidence of HCC incidence (1.39%). Patients with APRI >2 had an annual HCC incidence of 0.89% (95% CI, 0.87-0.91). A total of 3,906 patients (36.4%) had either cirrhosis codes or APRI >2 before SVR date, and in these patients, annual incidence of HCC was 0.83% (95% CI, 0.82-0.85).

HCC incidence was also higher among older (>65 years old; 0.95%), compared to younger, patients. There was a trend toward a higher HCC incidence rate in patients with genotype 3, HIV coinfection, alcohol use, diabetes, and elevated BMI; however, HRs were not statistically significant. Annual incidence of HCC occurred remained fairly stable through the first 5 years post-SVR, whereas there very few HCC cases recorded in years 6-8 to allow for precise estimation of risk (Table 2). The 5-year cumulative risk of HCC post-SVR was 0.33%.

The cumulative incidence steadily increased after SVR through year 8. Similar patterns were noted for subgroups of patients of different ages and with and without cirrhosis. The older age group had a higher cumulative incidence than younger patients (log-rank P value, <0.0001). There cumulative incidence of HCC was both higher with longer follow-up and with older age groups (Gray’s log-rank, P < 0.0001; Supporting Fig. S1). Patients with cirrhosis had a significantly higher cumulative incidence of HCC than patients without cirrhosis (Fig. 2; log-rank test P value, <0.0001).

**PREDICTORS OF HCC RISK POST-SVR**

In the multivariable Cox proportional hazards model, several risk factors were significant predictors of developing HCC post-SVR (Table 3). The highest risk of developing HCC was associated with presence of cirrhosis (adjusted HR = 6.69; 95% CI, 4.32-10.35). Patients with diabetes were almost 2 times more likely to develop HCC post-SVR than patients without diabetes (adjusted HR = 1.88; 95% CI, 1.21-2.91). In addition, patients with genotype 3 (adjusted HR = 1.62; 95% CI, 0.96-2.73) were more likely to develop HCC. Finally, patients who were older (age, 55-64: 2.04; 1.29-3.23 and age 65+: 4.51; 1.96-10.40 vs. 45-54 years old) and

FIG. 1. Study flow diagram with criteria used to identify the study cohort. Abbreviation: SVR12, SVR 12 weeks after end of treatment.
Hispanic ethnicity (adjusted HR, 2.27; 95% CI, 1.07-4.80) were more likely to develop HCC after having an SVR than younger and white patients. We further examined the effect of APRI score with or without cirrhosis diagnosis. High APRI (>2.0) in the presence of cirrhosis diagnosis was associated with the highest HCC risk (2% per year), compared to no cirrhosis and low APRI group (0.06% per year). HCC risk was
intermediate and equivalent with those who had a diagnosis of cirrhosis with low APRI (0.53% per year) or had had APRI but no cirrhosis diagnosis (0.48% per year; Supporting Table S1).

SECONDARY ANALYSES

We repeated the analysis excluding 35 HCC cases that developed during the first year of follow-up. Similar to the original analysis, the significant risk factors for HCC in this analysis remained cirrhosis, diabetes, Hispanic ethnicity, older age, and genotype 3 (Supporting Table S2), with cirrhosis as the strongest risk factor. We also estimated HCC incidence among patients with and without cirrhosis but restricted to patients with previous genotype 1 and 2, no baseline diabetes, and younger than 65 years. HCC was diagnosed in 31 cases during 2,552 PY follow-up in 981 patients with cirrhosis, for a relatively high incidence rate (1.215% per year; 95% CI, 1.167-1.262); however, it was low in those without cirrhosis, where a total of 25 HCC cases developed during 19,147 PY follow-up (in 6,673 patients with SVR and no cirrhosis pre-SVR for an incidence rate of 0.131; 95% CI, 0.129-0.132).

Discussion

This is the first large-scale U.S. cohort study to assess risk of HCC after achievement of SVR among patients with CHC. As expected, successful treatment led to a considerable reduction in HCC risk. However, annual risk of HCC among patients who cleared HCV was not negligible and ranged between 0.1% and 1.55% (overall, 0.33%) in various subgroups. The highest residual HCC risk was observed among patients with cirrhosis at the time of treatment (1.39% annual risk), followed by patients who achieved SVR after age 65 (0.95% annual risk) irrespective of cirrhosis. The presence or development of diabetes constituted a further significant risk factor for HCC, whereas having HCV genotype 3 before SVR was the only virological factor associated with increased HCC risk post-SVR. Risk of HCC appeared
to be constant for several years post-SVR. These findings have important implications for surveillance in the many patients who will achieve SVR with the new DAAs.

Our current findings argue strongly in favor of early treatment before development of cirrhosis and in implementing or continuing HCC surveillance among patients with cirrhosis even after achieving SVR. The best possible time to achieve SVR is before development of advanced fibrosis or cirrhosis. On the other hand, achieving SVR after development of cirrhosis was still associated with a significantly elevated HCC risk; that risk (1.39%) exceeded the 1% per year threshold for which some clinical practice guidelines advocate continue HCC surveillance. Having an APRI greater than 2.0 was also predictive of increased HCC risk, especially in those with documented cirrhosis (close to 2% per year), whereas absence of cirrhosis combined with low APRI was associated with the lowest risk of HCC in this cohort (0.06% per year); these two factors can be easily applied in clinical practice. Whereas older age at time of SVR was a major risk factor for HCC, annual incidence of HCC post SVR also seems to be constant over the first 5 years (Table 2), which argues against existing cancers before SVR, which would have been detected early on in follow-up, or solely aging-related cancer, which would been seen mostly in late years of follow-up.

Most previous studies that evaluated risk HCC factors post-SVR were conducted in Japan and included predominantly patients without cirrhosis. In these studies, the reported HCC incidence ranged from 1.5% to 5% in the first 5 years post-SVR. In our study, the 5-year rate was 0.33%. Ours is the largest study to date on HCC that was performed in Japan with a large number of patients with HCV cured and cirrhosis is likely to result in a number of patients with HCV cured and cirrhosis that is much larger than we have observed before. HCV genotype 3 was associated with higher HCC risk than other genotypes. Some of this observed association may be related to the known higher risk of cirrhosis with HCV genotype 3, and though we adjusted for cirrhosis, residual confounding by environment-gene joint effects, as well as misclassification (particularly of early stages of cirrhosis) were likely present.

The retrospective study design, though allowing for an efficient, well-powered study, was limited by diagnostic bias related to nonstandard use of testing or surveillance for HCC. However, given the relatively long follow-up, we believe that most HCCs in this cohort would have declared themselves within the study period. Similarly, misclassification was possible in potential risk factors of HCC (e.g., diabetes, obesity). We did not have information on duration of obesity, glycemic control in diabetes, or dose or duration of alcohol drinking. However, it was highly unlikely that patients with ongoing or severe alcohol use were treated with IFN, and therefore we do not believe that alcohol abuse was an important factor in this study. Although we had information on cirrhosis, we did not have more granular information on severity of hepatic fibrosis and no information on hepatic steatosis. HCC diagnosis may have been misclassified in some cases; however, of the 22 cases of the 100 HCCs that were chart-reviewed, 21 were verified as true HCC (i.e., PPV 95%). Whereas the study showed a beneficial effect of treatment in reducing HCC, selection bias related to who received the treatment was likely to be present. However, this was not the main purpose of the study; we rather focused on treated patients and compared those with SVR versus no SVR; this analysis eliminates the selection bias related to decision to treat. Last, the generalizability of the findings to nonveterans and women is unknown and will need to be examined in future studies. However, all patients who achieved SVR in this study did so with the use of IFN with or without RBV. It is not clear whether the same HCC risk reduction will be observed with SVR related to DAAs. It is possible that IFN-related antiproliferative properties would result in a greater HCC risk reduction than IFN-free DAAs.

An increasing number of patients are getting treated and cured of their CHC. Understanding the prognosis of these patients is timely as well as important. HCC risk was considerably and significantly lowered among those who achieved SVR than those who were treated but with no SVR. The high efficacy and safety of IFN-free DAA in patients with cirrhosis is likely to result in a number of patients with HCV cured and cirrhosis that is much larger than we have observed before.
We found in a large national VA cohort of patients who achieved SVR with IFN-based therapy have a considerably reduced risk compared to those treated with no SVR. However, the risk of HCC remains elevated for several years post-SVR, especially in subgroups of patients with cirrhosis, diabetes, and the elderly. These findings support early HCV treatment before development of cirrhosis and continued HCC surveillance even after SVR among those who already developed cirrhosis.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28535/supinfo.