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ORIGINAL ARTICLE

# HCC risk post-SVR with DAAs in East Asians: findings from the REAL-C cohort

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## Abstract

**Background** Despite HCV cure, patients remain at risk for HCC, but risk factor data for HCC following SVR are limited for Asian patients.

**Methods** To address this gap, we analyzed 5814 patients (5646 SVR, 168 non-SVR) from the Real-World Evidence from the Asia Liver Consortium for HCV (REAL-C) who did not have HCC or a history of HCC at baseline (pre-DAA treatment) and did not develop HCC within 6 months of baseline. To assess the effect of SVR on HCC incidence, we used 1:4 propensity score matching [(PSM), age, sex, baseline cirrhosis, and baseline AFP] to balance the SVR and non-SVR groups.

**Results** In the PSM cohort (160 non-SVR and 612 SVR), the HCC incidence rate per 100 person years was higher in the non-SVR compared to the SVR group (5.26 vs. 1.94, $p<0.001$). Achieving SVR was independently associated with decreased HCC risk (adjusted HR [aHR]: 0.41, $p=0.002$). Next, we stratified the SVR cohort of 5646 patients to cirrhotic and noncirrhotic subgroups. Among cirrhotic SVR patients, aged ≥ 60, having an albumin bilirubin grade (ALBI) of 2 or 3 (aHR: 2.5, $p<0.001$), and baseline AFP ≥ 10 ng/mL (aHR: 1.6, $p=0.001$) were associated with higher HCC risk, while among the non-cirrhotic SVR group, only baseline AFP ≥ 10 ng/mL was significant (aHR: 4.26, $p=0.005$).

**Conclusions** Achieving SVR decreases HCC risk; however, among East Asians, patients with elevated pretreatment AFP remained at risk. Pretreatment AFP, an easily obtained serum marker, may provide both prognostic and surveillance value for HCC in East Asian patients who obtained SVR.

**Keywords** Asia · Ethnicity · Liver cancer · Surveillance · Real-world · SVR · Treatment · HCV · AFP · Incidence

## Abbreviations

| | |
|---|---|
| HCV | Hepatitis C virus |
| HCC | Hepatocellular carcinoma |
| REAL-C | Real-World Evidence from the Asia Liver Consortium for HCV |
| DAA | Direct acting antiviral |
| ALBI | Albumin-bilirubin |
| PSM | Propensity score matching |
| AFP | Alpha-fetoprotein |
| SVR | Sustained virologic response |
| HR | Hazard ratio |
| CI | Confidence interval |

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## Introduction

Hepatitis C virus (HCV) was one of the leading causes of hepatocellular carcinoma (HCC) and liver related mortality until the advent of the new all oral antivirals (DAAs) introduced in 2014. In the DAA era, real-world HCV cure rates [sustained virologic response (SVR)] including those from Asia range between 85% and almost 100% depending on the HCV genotype, absent/presence of cirrhosis and active HCC [1]. As such, the numbers of patients requiring a liver transplant have fallen sharply as have the deaths associated with HCV [2].

However, the advent of DAA treatment has also brought into question whether a cure with DAA treatment decreases the risk for HCC such that HCC surveillance is no longer necessary. This is a very important question as research has shown that only 33% of all patients with HCC are actually diagnosed due to surveillance suggesting that there is poor adherence to the present guidelines [3]. Poor adherence is important as HCC has a very high mortality rate, less than 15% are still alive after 5 years attributed largely to late diagnosis with advanced stage that allows for only palliative care. Furthermore, though overall cancer deaths are decreasing, liver cancer is one of the cancers that are actually increasing around the world. Presently, it is the fourth leading cause of cancer deaths. The incidence of HCC is expected to increase 62% by 2040 if left unchecked [3, 4].

There have been a number of suggestions as to why there is poor adherence not the least of which include lack of knowledge and/or confusion about who should be surveilled [5]. Thus, it is important to better understand who remains at risk after successful DAA treatment so a targeted intervention to improve surveillance can be determined. Current studies have reported those who are older (> 50 years), have cirrhosis or a FIB-4 score > 3.25, have a lower albumin (< 4.4 g/dL) or increased liver stiffness measurement (LSM ≥ 20 kPa) remain at risk for HCC even after a HCV cure [6–9]. On the other hand, treatment and achievement of SVR in patients with HCV-related HCC actually improves survival by 60–70%, especially in patients with inactive HCC [7, 10–13]. However, many of these studies did not include patients with HCV from Asia, and data from large well controlled multinational studies from Asia are lacking.

This is particularly relevant because the vast majority of the world viremic HCV population reside in Asia [14]. Many studies from the Western world found risk for HCC is reduced after SVR, but there is a paucity of information from Asia. Therefore, using a large diverse population of patients with HCV from East Asia, we sought to determine the risk and risk factors associated with HCC after obtaining SVR with the use of the approved DAAs to better help guide HCC surveillance after SVR.

## Methods

### Study design and patient population

This was a retrospective study where patient data were extracted from the Real-World Evidence from the Asia Liver Consortium for HCV (REAL-C) database which has been described previously [10, 12, 13]. To date, the REAL-C registry has included 14 study centers in Hong Kong, Japan, South Korea, and Taiwan during the first phase of the registry (REAL-C I), and 15 Mainland China centers from the second phase (REAL-C II). Patients were identified through clinic/investigator databases. Eligible patient records were reviewed and the data were abstracted using a standardized Case Report Form by local study coordinators. The current study includes patients from REAL-C I who were followed approximately every 6 months with clinical, laboratory and ultrasound surveillance. Patients were divided into the SVR12 (HCV RNA < 25 IU/mL by a real-time reverse transcriptase PCR assay assessed at 12 weeks after the end of DAA treatment) and non-SVR12 groups. The primary outcome was incident HCC. Baseline (time zero) was defined as the date of DAA initiation.

The current study included adult (≥ 18 years) patients who were treated with any approved interferon-free DAA regimen between 2014 and 2018, had available SVR12 data and did not have a history of HCC at or within 6 months of DAA initiation. We excluded patients who were: (1) a recipient of a solid organ transplantation, (2) co-infected with human immunodeficiency virus or hepatitis B virus infection, (3) on significant doses of immunosuppression agents (prednisolone > 10 mg/day for > 4 weeks and all immunomodulatory agents and cancer chemotherapy, (4) terminally ill or moribund (prognosis of 12-month survival or less).

We determined cirrhosis status by liver histology, transient elastography (FibroScan®; Echosens, Paris, France) score > 12.5 kPa, FIB-4 > 3.25 [15], platelet count < $120 \times 10^3$/μL, imaging, endoscopic or clinical signs of cirrhosis and portal hypertension (nodular contour, ascites, splenomegaly, esophageal/gastric varices, ascites, variceal bleeding, and/or hepatic encephalopathy). HCC was diagnosed by cytology, histology or noninvasive criteria based on American Association for the Study of Liver Disease or Asian Pacific Association for the Study of the Liver [16, 17]. Patients were generally monitored every 6 months with liver ultrasound and serum AFP as per treating physicians.

### Statistical analysis

Frequency was compared between groups using the Chi-squared test for categorical variables and with Fisher's exact test when a frequency was noted to be less than five in a category. Groups means (presented as the mean ± standard deviation) were compared using the Student's *t* test and analysis of variance test if the data followed a normal distribution or the nonparametric Mann–Whitney *U* test if not. Patients were followed from the time of DAA initiation (baseline) until the date of death, date of last follow-up, or the date of HCC diagnosis for patients that developed HCC, whichever came first. HCC incidence rates were reported as per 100 person-years and 5-year cumulative incidence rates.

First, to balance background risks among the SVR and non-SVR groups, we performed 4:1 propensity score matching (PSM) where we estimated the effect of receiving DAA treatment by accounting for the covariates of age, sex, cirrhosis, and serum alpha-fetoprotein (AFP) using a caliper set at 0.25 standard deviation [18]. We then compared HCC incidence between the two groups. It is important to note, that to not overfit the model (as discussed below) which would reduce its generalizability [19], we performed PSM using only commonly collected variables [age, sex, cirrhosis, and baseline serum alpha-fetoprotein (AFP)]. In addition, we performed subgroup analysis for patients with cirrhosis and sensitivity analyses by excluding patients who developed HCC within 12 months of DAA initiation. To determine factors associated with incident HCC, we performed univariable and multivariable Cox regression models to estimate hazard ratio (HRs) and 95% confidence intervals (CIs). The selection of variables for the multivariable model was based on the significance (defined as $p < 0.1$) of variables in the univariable analysis along with previous clinical and research experience.

Second, we provided detailed subgroup data for the total SVR cohort regarding long-term HCC risk to guide future HCC surveillance. We estimated 5-year cumulative HCC incidence for all SVR patients, stratified by cirrhosis status plus additional stratification by baseline age, sex, albumin bilirubin (ALBI) grade, and baseline serum AFP levels by the highest quartile cutoff. In addition, we investigated factors associated with incident HCC among the cirrhotic SVR subgroup as well as for the non-cirrhotic SVR subgroup. Among the non-cirrhotic subgroup, we adjusted for fibrosis using the FIB-4 threshold of 1.45, below which patients had high probability of having no significant fibrosis [15]. We did not perform similar analyses for the non-SVR group due to the small sample size, but we presented individual clinical and laboratory characteristics of non-SVR patients who developed HCC but did not have cirrhosis for additional profiling.

All statistical analyses were performed using the STATA version 14 statistical package (College Station, TX, USA). Statistical significance was defined as a two-tailed *p* value of $< 0.05$.

## Results

### HCC incidence and associated factors in SVR versus non-SVR patients

#### Overall cohort

A total of 6661 patient records were reviewed and 5814 patients (168 non-SVR patients; 5646 SVR patients) met our study inclusion criteria and were included in our analysis (Supplemental Fig. 1). The non-SVR patients were significantly older, more likely female, more likely cirrhotic, and with higher pre-treatment FIB-4 or AFP levels (Table 1).

In total, there were 267 cases of incident HCC ($n = 23$ non-SVR; $n = 244$ SVR) over a median study follow-up of 2.93 years (IQR = 1.33–3.82 years). The incidence rate per 100 person-years was significantly higher for the non-SVR compared to the SVR group (4.95, 95% CI 3.29–7.45 vs. 1.66, 95% CI 1.47–1.88, $p < 0.001$), providing a 5-year cumulative incidence rate of 22.7% (95% CI 14.9–34.0) for the non-SVR and 8.3% (95% CI 6.6–10.4) for those who obtained SVR. Notably, the incidence rate did not appear to level off at year 5 (Supplemental Fig. 2).

#### PSM cohort

Due to significant differences in the SVR and non-SVR group, we performed a PSM where patients were matched on age, sex, baseline cirrhosis, and AFP, which yielded 160 pairs of well-matched non-SVR patients and 612 SVR patients (Table 2). The incidence rate per 100 person years was significantly higher in the non SVR group (5.26, 95% CI 3.50–7.92) compared to the SVR group (1.94, 95% CI 1.36–2.76, $p < 0.001$) (Fig. 1a). The 5-year cumulative incidence rates for the non-SVR and SVR groups were 23.97% (95% CI 15.8–35.3) and 7.55% (95% CI 5.3–10.7), respectively.

In subgroup analysis for patients with cirrhosis, there were 51 cases of HCC ($n = 22$ non SVR, $n = 29$ SVR). The incidence rate per 100 person years was significantly higher in the non-SVR group (8.59, 95% CI 5.66–13.05) compared to the SVR group (3.01, 95% CI 2.09–4.33, $p < 0.001$) (Fig. 1b), with similar findings in the sensitivity analysis where HCC cases that developed less than a year after DAA initiation were excluded (6.35, 95% CI 3.89–10.36 for non-SVR vs. 2.30, 95% CI 1.51–3.49 for SVR, $p = 0.002$). However, there was no difference in the HCC incidence rate per

**Table 1** Baseline characteristics of the overall cohort

| Characteristics | Non-SVR ($n=168$) | SVR ($n=5646$) | $p$ value |
|---|---|---|---|
| Age | 66.55 ± 12.12 | 64.20 ± 12.52 | 0.017 |
| Male | 56 (33.33) | 2404 (42.58) | 0.017 |
| Body mass index (kg/m$^2$) ($n=4439$) | 23.42 ± 3.31 | 23.37 ± 3.80 | 0.87 |
| Ethnicity | | | 0.063 |
| Chinese | 1 (0.60) | 156 (2.76) | |
| Taiwanese | 46 (27.38) | 1173 (20.76) | |
| Korean | 8 (4.76) | 472 (8.35) | |
| Japanese | 113 (67.26) | 3836 (67.89) | |
| Other | 0 (0) | 9 (0.16) | |
| Diabetes mellitus ($n=4923$) | 33 (21.29) | 881 (18.48) | 0.38 |
| HCV genotype ($n=5808$) | | | 0.82 |
| 1 | 116 (69.05) | 3937 (69.85) | |
| Non-1 | 52 (30.95) | 1699 (30.15) | |
| DAA treatment | | | < 0.001 |
| Sofosbuvir base | 79 (47.02) | 3704 (65.60) | |
| Non-Sofosbuvir base | 89 (52.98) | 1942 (34.40) | |
| FIB-4 score ($n=5737$) | 4.81 ± 3.91 | 3.81 ± 3.24 | < 0.001 |
| Cirrhosis | 105 (62.50) | 2911 (51.56) | 0.005 |
| CPT class ($n=1427$) | | | 0.59 |
| A | 32 (94.12) | 1314 (94.33) | |
| B/C | 2 (5.88) | 79 (5.67) | |
| MELD score ($n=1548$) | 8.61 ± 2.43 | 8.67 ± 3.61 | 0.92 |
| ALBI grade ($n=3016$) | | | 0.17 |
| 1 | 29 (27.62) | 992 (34.08) | |
| 2/3 | 76 (72.38) | 1919 (65.92) | |
| Aspartate aminotransferase (U/L) ($n=5763$) | 59.03 ± 43.25 | 56.91 ± 43.68 | 0.54 |
| Alanine aminotransferase (U/L) ($n=5808$) | 40 (25–76) | 41 (26–72) | 0.71 |
| Platelets ($10^9$/L) ($n=5784$) | 145.14 ± 65.77 | 163.64 ± 64.86 | < 0.001 |
| Albumin (g/dL) ($n=5726$) | 3.96 ± 0.48 | 4.09 ± 0.46 | < 0.001 |
| Total bilirubin (mg/dL) ($n=5653$) | 0.92 ± 0.50 | 0.84 ± 0.48 | 0.037 |
| Creatinine (mg/dL) ($n=5627$) | 0.71 (0.60–0.86) | 0.72 (0.60–0.89) | 0.16 |
| AFP (log10 ng/mL) ($n=5444$) | 0.83 ± 0.44 | 0.74 ± 0.42 | 0.009 |
| AFP (ng/mL) ($n=5444$) | | | 0.007 |
| < 10 | 111 (69.38) | 4139 (78.33) | |
| ≥ 10 | 49 (30.63) | 1145 (21.67) | |

*SVR* sustained virologic response, *DAA* direct-acting antiviral, *HCV* hepatitis C virus, *CPT* Child–Turcotte–Pugh, *MELD* model for end-stage liver disease, *ALBI* albumin-bilirubin, *AFP* alpha-fetoprotein

*Non-sofosbuvir group included: asunaprevir-based regimen ($n=1238$), ombitasvir/paritaprevir/ritonavir/dasabuvir combination ($n=544$), elbasvir/grazoprevir ($n=164$), glecaprevir/pibrentasvir ($n=58$), and other DAA ($n=27$)

100 years between the non SVR (0.55, 95% CI 0.08–3.93) and the SVR group (0.32, 95% CI 0.08–1.26, $p=0.60$) among patients without cirrhosis.

In multivariable analysis adjusted for study center and diabetes, achieving SVR was the only variable significantly associated with a decreased risk of developing HCC (aHR: 0.41, 95% CI 0.2–0.7, $p=0.002$) (Table 3), with also similar findings in the sensitivity analysis wherein HCC cases that developed less than a year after DAA initiation were excluded (aHR: 0.50, 95% CI 0.26–0.97, $p=0.041$).

## Subgroup HCC incidence and associated factors in SVR patients

To further examine HCC risk post-SVR, we grouped SVR patients in our total study cohort (5646 of 5814 patients) into subgroups: A cirrhosis subgroup and a non-cirrhosis subgroup, then further stratified them by age, sex, ALBI (for cirrhosis) or FIB-4 (for non-cirrhosis) and baseline (pre-DAA treatment) serum AFP levels.

**Table 2** Baseline characteristics of the propensity score matched cohort

| Characteristics | Non-SVR ($n=160$) | SVR ($n=612$) | $p$ value |
|---|---|---|---|
| Age | 66.76 ± 12.29 | 66.94 ± 11.28 | 0.86 |
| Male | 55 (34.38) | 196 (32.03) | 0.57 |
| Body mass index (kg/m$^2$) ($n=616$) | 23.39 ± 3.33 | 23.24 ± 3.59 | 0.67 |
| Ethnicity | | | 0.13 |
| Chinese | 1 (0.63) | 16 (2.61) | |
| Taiwanese | 46 (28.75) | 134 (21.90) | |
| Korean | 5 (3.13) | 31 (5.07) | |
| Japanese | 108 (67.50) | 431 (70.42) | |
| Diabetes mellitus ($n=647$) | 30 (20.41) | 88 (17.60) | 0.44 |
| HCV genotype | | | 0.39 |
| 1 | 111 (69.38) | 445 (72.83) | |
| Non-1 | 49 (30.63) | 166 (27.17) | |
| DAA treatment | | | < 0.001 |
| Sofosbuvir base | 76 (47.50) | 392 (64.05) | |
| Non-Sofosbuvir base | 84 (52.50) | 220 (35.95) | |
| FIB-4 score ($n=762$) | 4.86 ± 3.98 | 4.28 ± 3.16 | 0.05 |
| Cirrhosis | 100 (62.50) | 390 (63.73) | 0.77 |
| CPT class ($n=195$) | | | 0.57 |
| A | 30 (93.75) | 154 (94.48) | |
| B/C | 2 (6.25) | 9 (5.52) | |
| MELD score ($n=224$) | 8.68 ± 2.47 | 8.75 ± 4.26 | 0.91 |
| ALBI grade ($n=490$) | | | 0.59 |
| 1 | 27 (27.00) | 116 (29.74) | |
| 2/3 | 73 (73.00) | 274 (70.26) | |
| Aspartate aminotransferase (U/L) ($n=767$) | 60.13 ± 43.99 | 60.27 ± 46.04 | 0.97 |
| Alanine aminotransferase (U/L) ($n=771$) | 41.5 (25–78) | 43 (26–77) | 0.58 |
| Platelets ($10^9$/L) ($n=767$) | 145.59 ± 65.71 | 152.86 ± 61.01 | 0.19 |
| Albumin (g/dL) ($n=754$) | 3.96 ± 0.49 | 4.03 ± 0.42 | 0.08 |
| Total bilirubin (mg/dL) ($n=760$) | 0.93 ± 0.51 | 0.85 ± 0.42 | 0.04 |
| Creatinine (mg/dL) ($n=758$) | 0.71 (0.60–0.87) | 0.71 (0.59–0.89) | 0.49 |
| AFP (log10 ng/mL) | 0.83 ± 0.44 | 0.79 ± 0.43 | 0.27 |
| AFP (ng/mL) | | | 0.31 |
| < 10 | 111 (69.38) | 449 (73.37) | |
| ≥ 10 | 49 (30.63) | 163 (36.63) | |

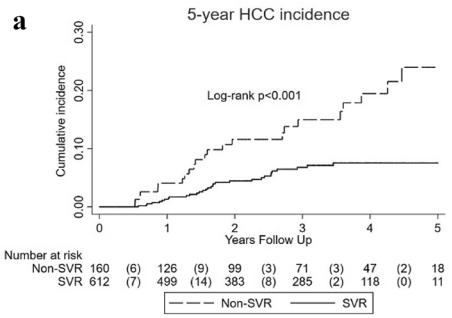
Patients were propensity score matched (1:4) using the caliper method on the following variables: age, sex, cirrhosis, and AFP

*SVR* sustained virologic response, *DAA* direct-acting antiviral, *HCV* hepatitis C virus, *CPT* Child–Turcotte–Pugh, *MELD* model for end-stage liver disease, *ALBI* albumin-bilirubin, *AFP* alpha-fetoprotein

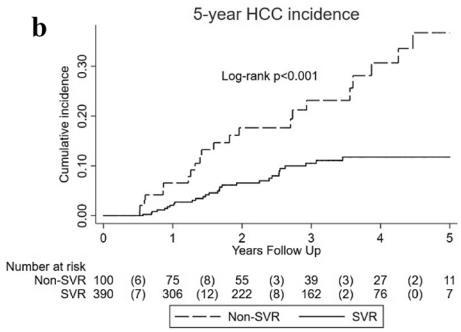
### Cirrhosis

Among patients with cirrhosis who achieved SVR (Table 4A), all subgroups had high 5-year cumulative HCC incidence rates above 10% (as high as 22.4%) except for those younger than 60 years or had ALBI grade 1. However, the 5-year cumulative HCC incidence rates in these two groups were still substantial, 6.06% (95% CI 3.50–10.40) for the younger than 60 years age group and 6.26% (95% CI 4.14–9.42) group with low ALBI grade 1. While the rate was highest among those with higher baseline AFP level ≥ 10 ng/mL (22.4, 95% CI 16.7–29.7), the 5-year cumulative incidence rate for those with AFP less than 10 ng/mL was still rather high at 9.95 (95% CI 8.16–12.10) (Table 4A).

On multivariable analysis, being 60 or 75 years or older (aHR: 2.32, 95% CI 1.4–3.9 or 2.9, 95% CI 1.7–4.9, $p=0.002$ or $<0.001$, respectively), having an ALBI grade of 2 or 3 (aHR: 2.5, 95% CI 1.7–3.8, $p<0.001$), and/or having an AFP ≥ 10 ng/mL (aHR: 1.6, 95% CI 1.2–2.1,




| Total (n=772) | | | | |
|---|---|---|---|---|
| HCC | Person years | Number of events | Incidence per 100 person years (95% CI) | 5-year cumulative incidence (95% CI) |
| Non-SVR | 436.95 | 23 | 5.26 (3.50-7.92) | 23.97 (15.83-35.32) |
| SVR | 1599.17 | 31 | 1.94 (1.36-2.76) | 7.55 (5.31-10.67) |




| Cirrhotic subgroup (n=490) | | | | |
|---|---|---|---|---|
| HCC | Person years | Number of events | Incidence per 100 person years (95% CI) | 5-year cumulative incidence (95% CI) |
| Non-SVR | 256.07 | 22 | 8.59 (5.66-13.05) | 36.74 (24.86-51.98) |
| SVR | 964.28 | 29 | 3.01 (2.09-4.33) | 11.79 (8.24-16.73) |

**Fig. 1** Five-year cumulative incidence of HCC in propensity score matched patients with SVR or without SVR (**a**), total (**b**) cirrhosis subgroup. Patients were propensity score matched (1:4) using the caliper method on the following variables: age, sex, cirrhosis, and AFP. *CI* confidence interval, *SVR* sustained virologic response, *HCC* hepatocellular carcinoma

**Table 3** Multivariable analysis for factors associated with incident HCC in patients with HCV from the propensity score matched cohort

| | Unadjusted HR (95% CI) | *p* value | Adjusted* HR (95% CI) | *p* value |
|---|---|---|---|---|
| HCV treatment status | | | | |
| Non-SVR | Referent | – | Referent | – |
| SVR | 0.36 (0.21–0.62) | < 0.001 | 0.41 (0.23–0.73) | 0.002 |
| Study center/region | | | | |
| Non-Japan | Referent | – | Referent | – |
| Japan | 1.22 (0.54–2.75) | 0.64 | 2.15 (0.75–6.13) | 0.15 |
| Diabetes mellitus | 1.47 (0.75–2.88) | 0.27 | 1.48 (0.75–2.92) | 0.26 |

Patients were propensity score matched using the caliper method on the following variables: age, sex, cirrhosis, and AFP

*HR* hazard ratio, *CI* confidence interval, *HCV* hepatitis C virus, *SVR* sustained virologic response

*Adjusted for HCV treatment status, study center, diabetes

$p = 0.001$) were all associated with having a significantly higher risk of developing HCC after adjusting for age, sex, ALBI grade, and AFP (Table 5A).

**Non-cirrhosis**

**Table 4** HCC incidence in SVR patients: (A) cirrhotic patients (B) noncirrhotic patients

| | *N* | Number of events | Incidence per 100 person years (95% CI) | Five-year cumulative incidence (95% CI) |
|---|---|---|---|---|
| (A) Cirrhotic patients | | | | |
| Overall | 2911 | 221 | 3.09 (2.71–3.53) | 14.90 (12.08–18.32) |
| Age | | | | |
| < 60 | 604 | 16 | 1.20 (0.73–1.96) | 6.06 (3.50–10.40) |
| 60–75 | 1482 | 117 | 3.17 (2.64–3.80) | 16.91 (12.46–22.72) |
| > 75 | 825 | 88 | 4.14 (3.36–5.11) | 16.07 (12.93–19.88) |
| Sex | | | | |
| Female | 1717 | 135 | 3.18 (3.69–3.76) | 16.11 (11.77–21.83) |
| Male | 1194 | 86 | 2.96 (2.40–3.66) | 13.44 (10.34–17.39) |
| ALBI grade | | | | |
| 1 | 992 | 29 | 1.24 (0.86–1.79) | 6.26 (4.14–9.42) |
| 2/3 | 1919 | 192 | 3.98 (3.46–4.59) | 18.61 (14.87–23.15) |
| AFP | | | | |
| < 10 | 1778 | 104 | 2.40 (1.98–2.91) | 9.95 (8.16–12.10) |
| ≥ 10 | 966 | 106 | 4.38 (3.62–5.30) | 22.44 (16.73–29.73) |
| (B) Noncirrhotic patients | | | | |
| Overall | 2735 | 23 | 0.31 (0.20–0.46) | 1.35 (0.88–2.06) |
| Age | | | | |
| < 60 | 1183 | 4 | 0.13 (0.05–0.35) | 0.46 (0.17–1.25) |
| 60–75 | 1277 | 16 | 0.44 (0.27–0.72) | 1.99 (1.19–3.30) |
| > 75 | 275 | 3 | 0.37 (0.12–1.15) | 1.60 (0.50–5.01) |
| Sex | | | | |
| Female | 1525 | 9 | 0.21 (0.11–0.41) | 0.86 (0.44–1.66) |
| Male | 1210 | 14 | 0.42 (0.25–0.71) | 1.96 (1.13–3.39) |
| Fib 4 | | | | |
| < 1.45 | 803 | 1 | 0.05 (0.01–0.34) | 0.13 (0.02–0.92) |
| ≥ 1.45 | 1932 | 22 | 0.40 (0.27–0.61) | 1.79 (1.16–2.75) |
| AFP | | | | |
| < 10 | 2361 | 18 | 0.27 (0.17–0.43) | 1.24 (0.76–2.00) |
| ≥ 10 | 179 | 5 | 1.10 (0.46–2.65) | 4.33 (1.82–10.14) |

*CI* confidence interval, *ALBI* albumin-bilirubin, *AFP* alpha-fetoprotein

Among the non-cirrhotic SVR patients, the overall 5-year cumulative incidence rate for HCC was below 1% for female, those with FIB-4 less than 1.45, and for those younger than 60 years; but the 5-year HCC rates were over 1% for all other subgroups, with most about 2% and highest for the subgroup with baseline AFP level ≥ 10 ng/mL (4.33%, 95% CI 1.8–10.1) (Table 4B).

On multivariable analysis adjusting for age, sex, FIB-4 score and AFP levels, only having an AFP ≥ 10 (aHR: 4.3, 95% CI 1.6–11.7, $P = 0.01$) was significantly associated with the development of HCC (Table 5B).

To shed further light onto the profile of non-cirrhotic patients who developed HCC despite achieving SVR, we provide detailed demographic, clinical and laboratory characteristics at DAA initiation of this lower risk sub-cohort in Supplemental Table 1A and B. While the majority of these incident HCC cases occurred in males and older patients, there were ten cases in females and four cases in patients in their mid-50s. Most were thin with a body mass index lower than 23 kg/m$^2$ and without diabetes mellitus. About half also occurred later, at least 2 years after receiving DAA therapy. In addition, most had normal serum albumin, AFP and platelet levels with many having platelet levels above $200 \times 10^9$/L, and most also had FIB-4 that was in the indeterminate range of 1.35–3.15.

## Discussion

In this study, we found among a large cohort of patients from East Asia who were treated and cured of their HCV that patients remained at risk for HCC though the risk was significantly less when compared to those who did not obtain a cure. After controlling for study center, diabetes, and HCV treatment status in our PSM cohort, we found that achieving SVR decreased the risk of HCC by 59%. These results also held in our sensitivity analyses when we excluded early incident HCC (within 12 months from DAA therapy).

Our results add and expand the current knowledge of the development of HCC after obtaining a cure for HCV [20–25]. First, to the best of our knowledge, our study is the largest multinational study of East Asians with long-term follow-up after DAA therapy. Since our study was comprised of a large and diverse cohort of patients with HCV from East Asia, we have confirmed prior findings from smaller studies and/or studies with limited follow-up that showed despite achieving a cure, patients with cirrhosis still remain at high risk for HCC which allows for more generalizability of these prior findings [22, 24, 25]. We also provided detailed subgroup HCC incidence risk for both cirrhotic and non-cirrhotic patients following SVR. As also shown by a prior study [6], the incidence of HCC did not level off by year 5 in our cohort, highlighting the need for continued long-term surveillance of at risk patients.

In our analysis of the SVR cirrhotic subgroup, we found the highest 5-year cumulative incidence of HCC was in those with an ALBI grade of 2 or 3 and those with an AFP ≥ 10, both at about 20%. Among the lowest risk subgroup, those younger than 60 years and those with ALBI grade of 1, the 5-year cumulative HCC rate for both of these two lower risk

**Table 5** Multivariable analysis for factors associated with incident HCC among the SVR subgroup of the overall cohort (A) cirrhotic patients (B) noncirrhotic patients

| | Unadjusted HR (95% CI) | *p* value | Adjusted* HR (95% CI) | *p* value |
|---|---|---|---|---|
| (A) Cirrhotic patients | | | | |
| Age | | | | |
| < 60 | Referent | – | Referent | – |
| 60–75 | 2.59 (1.53–4.36) | < 0.001 | 2.32 (1.37–3.91) | 0.002 |
| > 75 | 3.37 (1.98–5.74) | < 0.001 | 2.88 (1.68–4.93) | < 0.001 |
| Sex | | | | |
| Female | Referent | – | Referent | – |
| Male | 0.94 (0.72–1.23) | 0.65 | 0.94 (0.71–1.24) | 0.64 |
| ALBI grade | | | | |
| 1 | Referent | – | Referent | – |
| 2/3 | 3.13 (2.12–4.62) | < 0.001 | 2.51 (1.68–3.75) | < 0.001 |
| AFP (ng/mL) | | | | |
| < 10 | Referent | – | Referent | – |
| ≥ 10 | 1.82 (1.39–2.38) | < 0.001 | 1.57 (1.19–2.07) | 0.001 |
| (B) Noncirrhotic patients | | | | |
| Age | | | | |
| < 60 | Referent | – | Referent | – |
| 60–75 | 3.28 (1.10–9.81) | 0.034 | 2.39 (0.76–7.51) | 0.14 |
| > 75 | 2.74 (0.61–12.25) | 0.19 | 1.96 (0.41–9.29) | 0.39 |
| Sex | | | | |
| Female | Referent | – | Referent | – |
| Male | 1.96 (0.85–4.52) | 0.12 | 2.03 (0.88–4.69) | 0.097 |
| Fib 4 | | | | |
| < 1.45 | Referent | – | Referent | – |
| ≥ 1.45 | 8.25 (1.11–61.18) | 0.039 | 5.01 (0.62–40.23) | 0.13 |
| AFP (ng/mL) | | | | |
| < 10 | Referent | – | Referent | – |
| ≥ 10 | 4.12 (1.53–11.11) | 0.005 | 4.26 (1.55–11.70) | 0.005 |

*HR* hazard ratio, *CI* confidence interval, *AFP* alpha-fetoprotein, *ALBI* albumin-bilirubin

*(A) Adjusted for age, sex, ALBI grade, AFP

*(B) Adjusted for age, sex, FIB-4 score, AFP

groups was about 6%, slightly under the 1.5% annual risk threshold for HCC surveillance for cirrhotics [16]. However, this higher annual risk threshold for cirrhotics (as compared to non-cirrhotics) was based on pre-DAA cost-effectiveness studies which did not take into account the longer survival benefit derived from successful DAA treatment which may improve the cost-effectiveness ratio at a lower surveillance threshold.

More worrisome is the significant residual HCC risk among the non-cirrhotic SVR patient population. While our findings among non-cirrhotic SVR patients confirmed low risk (< 1% 5-year cumulative incidence) in patients younger than 60 years, female, and those with a very low FIB-4 (< 1.45) score, we noted the relatively high 5-year cumulative HCC incidence of 4.3% for non-cirrhotic SVR patients who had an elevated baseline AFP, which exceeds the HCC surveillance risk threshold of about 0.2% per year suggesting that it can be cost-effective to perform HCC surveillance in this high-risk group such that continued surveillance should be considered. In our detailed examination of the 23 non-cirrhotic SVR patients who developed incident HCC following SVR, we found incident HCC patients to include those younger than 60 or female or had a normal platelet count as well as having a FIB-4 score which fell into the indeterminate range, which is contrary to a recent study which suggested that continued HCC surveillance should be considered for those whose FIB-4 score is > 3.25 [6]. Our results may be different due to the population characteristics of study where Ioannou et al.'s study consisted of almost all male (97.2%) whereas our population was less than 50% male [6]. The difference in our findings further highlights the importance of our study whereby we have shown that certain criteria cannot simply be extrapolated to different ethnic groups.

For patients with cirrhosis and SVR, we suggest that the ALBI score and baseline AFP level may provide results

which are beneficial to use for prognosis when evaluating patients from East Asia who may be at a higher risk for the development of HCC. Our results regarding ALBI score are in line with prior studies showing the ALBI score as a marker of hepatic function which has excellent correlation with prognosis in HCC patients undergoing a variety of treatment modalities and in different settings [26, 27].

There were several strengths of our study. First, we used several analytic approaches (PSM and subgroup, sensitivity, and stratified) to control for the noninterventional/nonrandomized nature of the study. As such, our findings remained consistent throughout all these different analyses suggesting that our results are robust. There are limitations as well which come from using data from multiple sites. However, we took many precautions to overcome these obstacles by using a standardized data collection form, unifying definition of data variables, and having a central data depository and quality control. In addition, we were unable to account for the effect of alcohol on the development of HCC due to missing data on alcohol usage. However, according to a recent report by Gilligan et al. [28], estimates of alcohol usage by self-report are often inaccurate, and thus the added value of this factor is unclear.

In summary, our study confirmed that achievement of SVR was independently associated with a 59% reduction in HCC risk in a large East Asian cohort. However, significant risk for HCC remained after SVR with a 5-year cumulative HCC incidence of approximately 8% overall; 12% for cirrhotic patients which could be as high as 20% if the ALBI grade was 2/3 and 22% if pre-treatment AFP is elevated. For patients without known cirrhosis, the 5-year cumulative incidence approached 2% for patients aged ≥ 60 years or FIB-4 ≥ 1.45 and over 4% with an elevated pre-treatment AFP. Thus, in East Asian patients who obtain SVR, consideration should be given to reviewing pre-treatment AFP levels when determining post-SVR HCC surveillance regardless of cirrhosis status.

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## Compliance with ethical standards

**Conflict of interest** YT: Research support: Janssen, Gilead, Speaker: Gilead. CFH: Speaker: AbbVie, BMS, Gilead, Merck. YCH: Research support: Gilead, Consultation: Gilead, Speaker: AbbVie, Bristol-Myers Squibb and Gilead. ME: Speaker: AbbVie. DHL: Research support: Gilead Sciences Korea, Korea Pharma. GW: Research support: Gilead, Consultation: Gilead, Speaker: Abbott, AbbVie, BMS, Echosens, Furui, Gilead, Janssen and Roche, Research grant: Gilead. MFY: Consultation: AbbVie, Arbutus Biopharma, Assembly Biosciences, Bristol Myer Squibb, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceutical. YU: Research support: Gilead, AbbVie, Governmental funding for research: AMED. YE: Speaker: Gilead. MLY: Research support: Abbott, BMS, Gilead and Merck, Consultant and/or an advisory board: Abbvie, Abbott, Ascletis, BMS, Gilead and Merck, Speaker: Abbvie, Abbott, BMS, Gilead, Merck, and IPSEN. WLC: Consultation: Gilead, AbbVie, BMS, MSD, PharmaEssentia, Speaker: Gilead, AbbVie, BMS, MSD, PharmaEssentia. CYD: Consultation: Abbvie, Speaker: AbbVie, Merck, BMS, and Gilead. MHL: Research support: The Ministry of Science and Technology, Taipei, Taiwan (105-2628-B010-003-MY4, 107-2314-B-010-004-MY2 and 107-2918-I-010-004), Consultation: Gilead. MHN: Research support: Enanta, Gilead, Pfizer, B.K. Kee Foundation, National Cancer Institute. Consultant and/or an advisory board: Novartis, Bayer, Eisai, Intercept, Gilead, Janssen, Laboratory of Advanced Medicine, Exact Sciences, and Intercept. All other authors have nothing to disclose.

**Statement of ethics** The study was conducted in accordance with the ethics principles of the Declaration of Helsinki in 1975, as revised in 2008, and was approved by the Institutional Review Board of Stanford University, Stanford, California, USA and at each participating study center.

## References


1. Huang CF, Iio E, Jun DW, et al. Direct-acting antivirals in East Asian hepatitis C patients: real-world experience from the REAL-C Consortium. Hepatol Int. 2019;13:587–98.
2. Bodzin AS, Baker TB. Liver transplantation today: where we are now and where we are going. Liver Transpl. 2018;24:1470–5.
3. Zhao C, Jin M, Le RH, et al. Poor adherence to hepatocellular carcinoma surveillance: a systematic review and meta-analysis of a complex issue. Liver Int. 2018;38:503–14.
4. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
5. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer tomorrow. In: Lyon, France: International Agency for Research on Cancer; 2018.
6. Ioannou GN, Beste LA, Green PK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. Gastroenterology. 2019;157:1264-1278 e1264.
7. Janjua NZ, Chong M, Kuo M, et al. Long-term effect of sustained virological response on hepatocellular carcinoma in patients with hepatitis C in Canada. J Hepatol. 2017;66:504–13.
8. Kanwal F, Kramer JR, Asch SM, et al. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. Hepatology. 2020;71:44–55.
9. van der Meer AJ, Feld JJ, Hofer H, et al. Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication. J Hepatol. 2017;66:485–93.
10. Dang H, Yeo YH, Yasuda S, et al. Cure with interferon-free direct-acting antiviral is associated with increased survival in patients with hepatitis C virus-related hepatocellular carcinoma from both east and west. Hepatology. 2020;71:1910–22.
11. Ide T, Koga H, Nakano M, et al. Direct-acting antiviral agents do not increase the incidence of hepatocellular carcinoma development: a prospective, multicenter study. Hepatol Int. 2019;13:293–301.
12. Ogawa E, Toyoda H, Iio E, et al. HCV cure rates are reduced in patients with active but not inactive hepatocellular carcinoma- a practice implication. Clin Infect Dis. 2019. https://doi.org/10.1093/cid/ciz1160.
13. Waziry R, Hajarizadeh B, Grebely J, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression. J Hepatol. 2017;67:1204–12.
14. Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2:161–76.
15. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43:1317–25.
16. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67:358–80.
17. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11:317–70.
18. Rosenbaum RP, Rubin BD. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41–55.
19. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004;66:411–21.
20. Calvaruso V, Cabibbo G, Cacciola I, et al. Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis treated with direct-acting antiviral agents. Gastroenterology. 2018;155:411-421 e414.
21. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019;393:1453–64.
22. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65:727–33.
23. Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology. 2017;153:996-1005 e1001.
24. Romano A, Angeli P, Piovesan S, et al. Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: a prospective population study. J Hepatol. 2018;69:345–52.
25. Singal AG, Lim JK, Kanwal F. AGA clinical practice update on interaction between oral direct-acting antivirals for chronic hepatitis C infection and hepatocellular carcinoma: expert review. Gastroenterology. 2019;156:2149–57.
26. Hiraoka A, Kumada T, Michitaka K, et al. Newly proposed ALBI grade and ALBI-T score as tools for assessment of hepatic function and prognosis in hepatocellular carcinoma patients. Liver Cancer. 2019;8:312–25.
27. Ioannou GN, Green PK, Beste LA, et al. Development of models estimating the risk of hepatocellular carcinoma after antiviral treatment for hepatitis C. J Hepatol. 2018;69:1088–98.
28. Gilligan C, Anderson KG, Ladd BO, et al. Inaccuracies in survey reporting of alcohol consumption. BMC Public Health. 2019;19:1639.




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