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【 ORIGINAL ARTICLE 】

The Impact of Antiviral Therapy for Hepatitis C Virus on the Survival of Patients after Hepatocellular Carcinoma Treatment

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Abstract:

Objective Owing to advances in direct-acting antiviral (DAA) therapy, a considerable number of patients with hepatitis C virus (HCV)-positive hepatocellular carcinoma (HCC) are now able to achieve a sustained viral response (SVR) after curative treatment of HCC. However, the beneficial effect of a DAA-SVR on the survival remains unclear.

Methods A total of 205 patients with HCC who were HCV-positive with Child-Pugh A at the onset from 2008 to 2018 were categorized into 2 groups: 140 patients untreated for HCV throughout the entire course after HCC development (untreated group) and 65 patients treated for HCV with DAAs following HCC treatment who achieved an SVR (SVR group). After propensity score matching, 63 patients from each group were selected. Using these patients, the survival and maintenance of Child-Pugh A after HCC treatment were compared between the untreated group and SVR group.

Results There was a significant difference in the overall survival ($p<0.001$) and the rate of maintaining Child-Pugh A ($p<0.001$) between the groups. The 5-year survival rates were 96% (SVR group) and 60% (untreated group), and the proportions of patients with Child-Pugh A at 5 years after HCC treatment were 96% (SVR group) and 38% (untreated group).

Conclusion In patients with HCV-positive HCC, achieving a DAA-SVR after HCC treatment significantly improved the overall survival rate compared with HCV-untreated patients. The contribution of DAA-SVR during the course of HCC treatment to a longer survival is mainly due to the prevention of the progression of Child-Pugh A to B/C. Further research is needed to determine whether aggressive antiviral therapy is also effective for HCC patients with Child-Pugh B/C.

Key words: direct-acting antiviral, hepatitis C, hepatocellular carcinoma

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Introduction

The Global Hepatitis Report of the World Health Organization (WHO) states that hepatitis C virus (HCV) has infected 1% of the population worldwide (71 million) and causes approximately 400,000 deaths annually, mainly from cirrhosis and hepatocellular carcinoma (HCC) (1). HCV is a leading cause of chronic liver disease and HCC globally (2, 3). Chronic HCV infection is the second-most common risk factor for HCC and is responsible for 10-25% of all HCC cases (4). Over 20-30 years, 20-30% of patients with chronic HCV infections will develop cirrhosis and end-stage liver disease, and 1-4% of these patients will progress to HCC each year (5, 6). A total of 80-90% HCV-related HCC cases occur in the setting of cirrhosis (7). Several stud-

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ies have indicated the importance of HCV management in HCC therapeutic care and prevention (8, 9).

Despite technological and therapeutic advances, HCC is one of the few cancers with an increasing incidence and a dismal 5-year survival rate of only 18.1%, according to a 2017 report (10). Indeed, recent studies concerning systemic palliative therapies for HCC have reported only a modest survival advantage from palliative treatment, with a median overall survival (OS) of about 10-13 months in treated patients compared with 7-8 months in placebo groups (11).

The major current therapeutic goal for HCV and prevention of liver disease progression is a sustained viral response (SVR), which is defined by negative HCV RNA results at 12 weeks post-treatment (SVR12) that appears to be durable, with a late virologic relapse rate of less than 1% (12, 13). Therapeutic management of HCV has recently shifted from interferon (IFN)-based therapies to all-oral IFN-free direct-acting antiviral (DAA) combination regimens. IFN-free DAAs have been shown to be a highly effective (> 80-90% cure rate) and well-tolerated treatment, even for patients with advanced liver disease, including HCC (14-19). Owing to advances in DAA therapy, a considerable number of patients with HCV-positive HCC can achieve an SVR after curative treatment of HCC. Findings of observation studies in patients with HCV infection have shown a reduced risk for HCC, complications of liver disease, and mortality in patients treated with IFN or DAAs who achieved an SVR (20, 21). However, the beneficial effect of a DAA-SVR on the survival of such patients remains unclear.

There is controversy concerning the reduction in early HCC occurrence and recurrence after all-oral DAA therapies (22-28). The early recurrence rate of liver cancer after DAA therapy varies markedly among reports (12.7-28.8%). Conti et al. reported that the 6-month recurrence rate was 28.8% (22); in contrast, the ANRS study group reported that 26 (12.7%) of 189 HCC patients experienced recurrence over 20.2 months of median follow-up (28).

We herein report the impact of antiviral therapy for HCV on the survival of HCC patients after treatment of HCC. The main aim of this study was to clarify whether or not DAAs prolong the OS in patients with HCV-related compensated cirrhosis and a first diagnosis of HCC (without a history of HCC recurrence before DAA treatment). We used an appropriately matched control group of patients who had not received DAAs for this comparison. The secondary outcomes were to elucidate the impact of DAAs on HCC recurrence and hepatic decompensation.

Materials and Methods

Study design and patient population

This study met the ethical guidelines of the Declaration of Helsinki. This was a retrospective cohort study using data from the University of Yamanashi. This study protocol was approved by the Institutional Review Board.

We included 375 adult patients with who had been diagnosed with HCV-related HCC in this study (Fig. 1). After excluding patients who were ineligible, 205 patients (untreated group: 140; SVR group: 65) who were newly diagnosed with HCV-positive HCC between 2008 to 2018 and maintained Child-Pugh A were analyzed for baseline characteristics. Those patients were classified into 2 groups: 140 untreated for HCV (untreated group) and 65 treated for HCV with DAAs after HCC therapy and who achieved an SVR (SVR group) (Fig. 1).

To balance the two study groups (patients untreated for HCV and patients with SVR), propensity score matching (PSM), including the age, sex, diabetes mellitus (DM), body mass index (BMI), alcohol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), estimated glomerular filtration rate (eGFR), alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKAII), platelet count, prothrombin activity value (PT), Child-Pugh score, and clinical stage of HCC, was performed. After PSM, 63 patients from each group were selected (Fig. 1). The baseline characteristics of the 63 pairs of matched patients from the 2 study groups (63 DAA-untreated for HCV and 63 SVR) are shown in Table 1. Matching produced a balance in most of the baseline variables between the 63 patients treated with DAAs (SVR group) and the 63 controls who did not receive DAAs (untreated group). Using these patients, the survival and maintenance of Child-Pugh A after HCC therapy were compared between the groups.

Definitions

HCV diagnoses were determined by positive HCV RNA polymerase chain reaction or HCV antibody tests, a history of anti-HCV therapy, or a documented history of HCV from physicians' notes. HCC diagnoses were confirmed through radiology or pathology reports based on the American Association for the Study of Liver Diseases diagnosis guidelines (15). An SVR was determined based on the confirmation of undetectable HCV RNA (limit of detection of 25 IU/mL) 12 weeks after the treatment end date.

Statistical analyses

Continuous variables are expressed as means and ranges, while categorical data are reported as counts and percentages. The Kaplan-Meier estimator was used to estimate the OS, time to HCC recurrence, and time to liver decompensation. Log-rank tests were used to assess the differences in these outcomes. Cox regression analyses were used to identify variables associated with mortality, HCC recurrence, and hepatic decompensation in the DAA group. Data analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and Microsoft Excel 2016 Data Analysis (version 3.20), a custom software program based on Python v. 3.52 (Python Software Foundation, Wolfeboro Falls, USA) using the Scikit-learn library (29). $p < 0.05$ was used to determine significance.

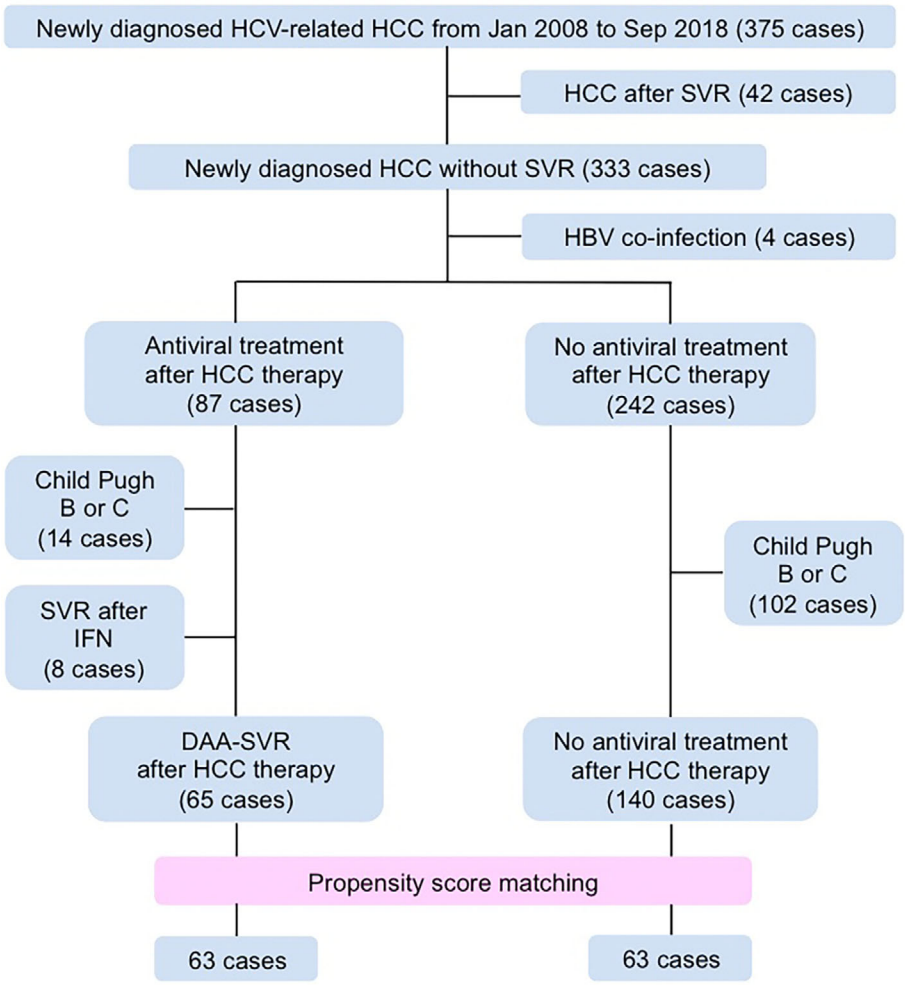

Figure 1. Flowchart of the study. A flowchart of the study for the inclusion and exclusion of patients is shown. Propensity score matching was performed on the following variables: age, sex, DM, BMI, alcohol, ALT, AST, eGFR, AFP, PIVKA, platelet count, prothrombin time, Child-Pugh score, and clinical stage of HCC. HBV: hepatitis B virus

Results

Recurrence of HCC and its therapy in patients of the DAA-SVR group (n=63) and untreated group (n=63) are shown (Fig. 2). Since early recurrence may be related to the initial tumor status, and the impact of antiviral therapy may be small in early recurrence, we examined the status of first and second HCC recurrence in these two groups. As shown in Supplementary material 1 (a), there was no significant difference in the first and second HCC recurrence rates between the two groups. To further evaluate the initial HCC status in these groups, we also examined the status of first and second HCC recurrence and the dropout rate from the up-to-seven criteria in patients with Barcelona Clinic Liver Cancer-Stage A at the initial diagnosis. As shown in Supplementary material 1 (b), there was no significant difference in the first and second HCC recurrence rate and the dropout rate from the up-to-seven criteria in the two groups, indicating that the initial HCC status was similar between those two groups.

However, when the cumulative number of HCC treatments (=recurrences) per year was examined, there was a significant difference between the DAA-SVR group and untreated group (average 0.56 vs. 0.94, $p<0.001$, Fig. 2), demonstrating that the cumulative number of treatments (recurrences) per year was significantly lower in the DAA-SVR group than in the untreated group. This finding suggested that recurrence was more frequent in the later stage in the untreated group than in the DAA-SVR group. To further investigate factors affecting recurrence, we examined the treatment procedures selected at the time of recurrence between the DAA-SVR group and untreated group and found that there was a significant difference in the treatment procedures between the groups, and curative procedures were selected more frequently in the DAA-SVR group than in the untreated group (Supplementary material 2).

During the observation period, 3 of 63 patients (4.8%) in the SVR group and 27 of 63 patients (42.9%) in the untreated group died. There was a significant difference in the OS between these groups ($p<0.001$, log-rank test) (Fig. 3). The 5-year survival rate was 96% in the DAA-SVR group

Table 1. Baseline Characteristics of 126 Patients between the DAA-SVR Group and Untreated Group.

	No antiviral treatment after HCC therapy (n=63)	DAA-SVR after HCC therapy (n=63)	p value
Gender (M/F)	39/24	45/18	0.345
Age (years)	71 (50-85)	68 (48-81)	0.109
Obesity (BMI>25)	18 (29%)	17 (27%)	1.000
Alcohol abuse	23 (37%)	25 (40%)	0.855
Diabetes	18 (29%)	24 (38%)	0.345
Platelet count ($10^4/\mu L$)	11.4 (4.8-23.0)	12.8 (3.2-29.9)	0.183
PT (%)	80.4 (60.4-103)	82.4 (57.4-106)	0.141
AST (IU/L)	49 (24-125)	51 (17-234)	0.961
ALT (IU/L)	49 (12-166)	47 (10-384)	0.678
eGFR (mL/min/1.73 m^2)	71.0 (14.0-110.5)	74.2 (8.6-138.8)	0.287
PIVKAII (mAU/mL)	26 (8-4620)	20 (8-17521)	0.420
AFP (ng/mL)	19.5 (1.6-1128.9)	12.2 (1.4-2812.1)	0.540
Child-Pugh score (5/6)	40/23	46/17	0.339
Stage (I/II/III)	22/33/8	25/33/5	0.643
BCLC (0/A/B/C/D)	0/42/21/0/0	0/36/27/0/0	0.359
Tumor number	1.4 (1-25)	2.4 (1-4)	0.049
Tumor size (mm)	19.5 (9-60)	22.6 (10-38)	0.079
FIB-4 index	5.5 (2.1-14.8)	4.6 (1.4-12.8)	0.077
Observation duration (year)	3.3	5.1	0.021

Comparison performed after propensity score matching. Values are shown as mean (range) or numbers (%). In the observation duration, values are shown as median. The t-test for continuous variables and the chi-squared test for categorical variables were used to compare them between DAA and no DAA groups.

BMI: body mass index, PT: prothrombin activity value, ALT: alanine transaminase, AST: aspartate aminotransferase, eGFR: estimated glomerular filtration rate, PIVKAII: protein induced by vitamin K absence or antagonist-II, AFP: alfa-fetoprotein, BCLC: Barcelona Clinic Liver Cancer, HCC: hepatocellular carcinoma, DAA: direct-acting antivirals, SVR: sustained viral response

and 60% in the untreated group. In the multivariate analysis, the DAA-SVR was extracted as the independent variable most strongly associated with the OS ($p<0.005$, the Cox proportional hazard analysis) (Table 2). Supplementary material 3 shows the causes of death, indicating no marked difference in liver-related deaths between the DAA-SVR group (1/3, 30%) and the untreated group (15/27, 56%) ($p=0.586$).

Regarding the maintenance of Child-Pugh A after HCC therapy, 2 of 63 patients (3.2%) in the DAA-SVR group and 34 of 63 patients (54.0%) in the untreated group showed exacerbation to Child-Pugh B/C during the observation period (Fig. 4). There was a significant difference in the rate of maintaining Child-Pugh A between the untreated and DAA-SVR groups ($p<0.001$, log-rank test, Fig. 4, 5), and the proportion of patients with Child-Pugh A at 5 years after HCC treatment was 96% in the DAA-SVR group and 38% in the untreated group.

Discussion

A considerable number of patients with HCV-positive HCC are able to achieve an SVR after curative treatment of HCC with DAA therapy. Findings of observation studies in patients with HCV infection have shown a reduced risk for HCC, complications of liver disease, and mortality in patients treated with IFN or DAAs who achieved an SVR. However, the beneficial effect of DAA-SVR on patient survival after continue treatment of HCC remains unclear.

Antiviral therapy for chronic hepatitis C has progressed markedly, starting with IFN monotherapy, followed by peginterferon (PEG-IFN) and ribavirin (RBV) combination therapy (PEG-IFN/RBV), DAA, PEG-IFN and RBV combination therapy (PEG-IFN/RBV/DAA), and IFN-free DAA combination therapy, resulting in high SVR rates. With advances in antiviral therapies, high-risk elderly patients or patients with advanced liver fibrosis are now able to receive antiviral therapy and achieve an SVR safely. However, considering the backgrounds of those patients, SVR patients are still considered at risk of developing HCC.

In a cohort study at a single institute, Ikeda et al. reported that the 5- and 10-year cumulative carcinogenic rates were 3.3% and 11.1%, respectively, for 1,056 patients who achieved an SVR (median age, 50 years old), and the carcinogenic rate was 0.56/100 person-years (30). Similarly, Arase et al. reported that the 5-year cumulative carcinogenic rate was 2.8% for 1,900 patients who achieved an SVR, while the carcinogenic rate in patients with cirrhosis (1.82/100 person-years) was significantly higher than for those with chronic hepatitis (0.16/100 person-years) (31). Sugiura et al. reported that a history of HCC was an independent risk factor of treatment failure in patients with chronic HCV infection receiving DAAs (32).

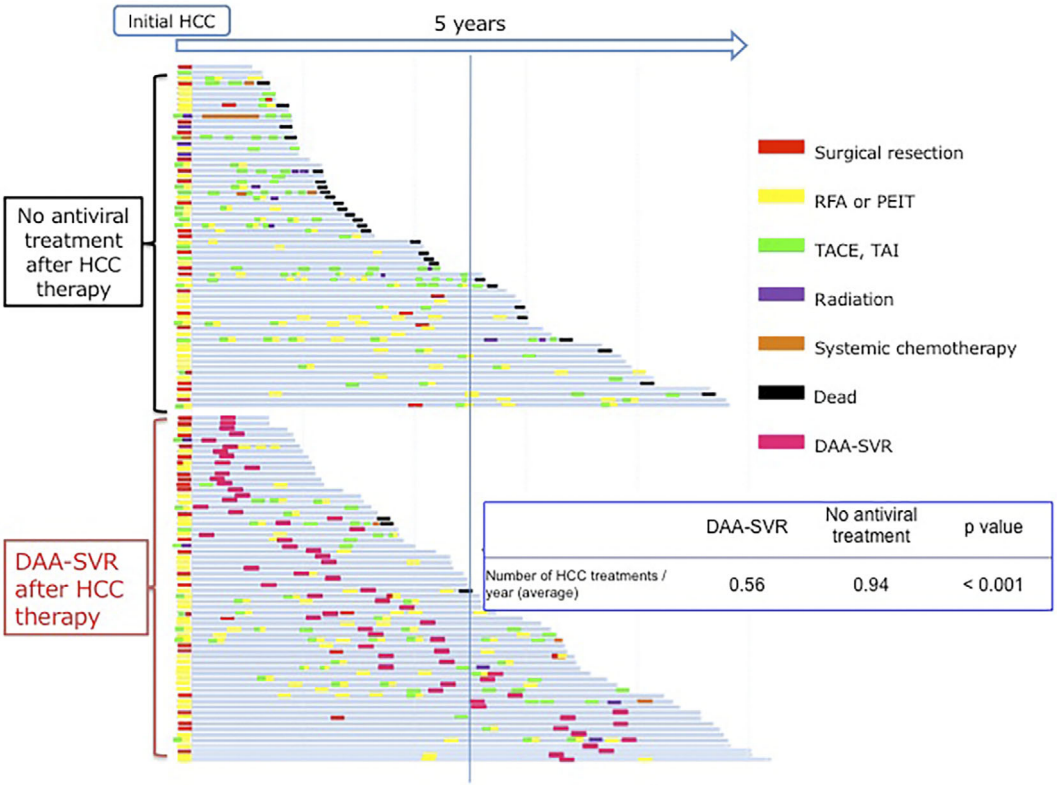

Figure 2. **HCC recurrence and its therapy in the DAA-SVR and untreated groups. The rate of recurrence of HCC and its therapy in the DAA-SVR group (n=63) and untreated group (n=63) is shown. There was a significant difference in the number of HCC treatments per year between the DAA-SVR group and untreated group (shown as an average). HCC: hepatocellular carcinoma, DAA: direct-acting antiviral, SVR: sustained viral response, RFA: radiofrequency ablation, PEIT: percutaneous ethanol injection, TACE: transcatheter arterial chemoembolization, TAI: transhepatic arterial infusion**

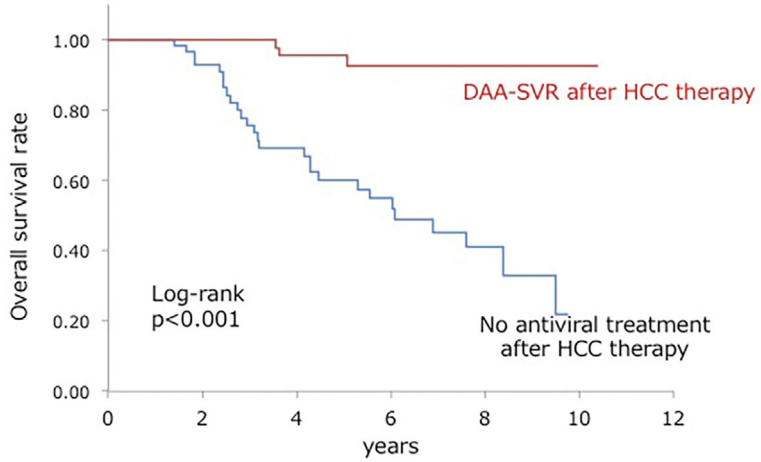

Figure 3. **The overall survival of HCC patients of the DAA-SVR group and untreated group. The overall survival rates after HCC therapy of 63 patients treated with DAAs (DAA-SVR after HCC therapy) and 63 patients who did not receive DAAs (no antiviral treatment after HCC therapy) after propensity score matching are shown. The Kaplan-Meier method was used to assess the overall survival rates, and the log-rank test was used to compare them. HCC: hepatocellular carcinoma, DAA: direct-acting antiviral, SVR: sustained viral response**

Most investigators and clinicians now accept DAAs as the standard of care, even for patients with advanced liver disease and a history of HCC (33, 34). It is therefore not feasible to design randomized controlled study for the direct

comparison of patients who did and did not receive DAAs. DAA and no DAA groups may thus be compared only by propensity score methods to correct for potential confounding.

Our study suggested that the improvement in the survival was caused by a reduction in the progression of hepatic decompensation due to SVR. The findings presented above strongly support the current practice of DAA treatment, even in patients with advanced liver disease and HCC. Clarifying the mechanism underlying the observed reduction in mortality associated with DAAs is a goal of the present study. We speculate that DAAs improve the OS through the long-term preservation of the liver functn, resulting in a greater likelihood that those patients will be able to receive curative treatment. However, we also speculate that untreated patients are forced to receive more damaging non-curative treatments, such as transarterial embolization and systemic chemotherapy, as a result of their poor liver reserve, which may further worsen their liver reserve and reduce the OS. Although the risk of HCC recurrence remains high, the inefficacy of DAA treatment on HCC recurrence risk may be able to be overcome via the proven survival-enhancing benefit with regard to hepatic decompensation (35). Similar to the present study, Singal et al. also suggested that DAA therapy was associated with a significant reduction in the risk of death in their analysis of nearly 800 patients with a complete response to HCC treatment (36).

Huang et al. reported that DAA use does not change the risk of HCC recurrence after local-regional therapy among waitlisted patients but is rather associated with a reduced risk of waitlist dropout due to tumor progression or death (34). Although waitlisted patients had more advanced liver disease (half had Child-Pugh B or C cirrhosis) compared to our cohort of compensated cirrhotic patients, these results add further evidence that DAAs reduce the risk of decompensating events even in patients with advanced liver disease and HCC. Some studies have suggested that DAA

Table 2. Multivariate Analysis for Clinical Factors Associated with Overall Survival.

	HR (95%Cl)	p value
Age (years)	1.01 (0.96-1.07)	0.63
PT (%)	0.99 (0.95-1.04)	0.82
DAA-SVR	0.11 (0.03-0.37)	<0.01
Tumor number	1.12 (1.00-1.26)	0.047
Tumor size (mm)	1.04 (0.99-1.09)	0.10
FIB-4 index	1.07 (0.94-1.22)	0.30

Cox proportional hazards regression analysis was used to extract the independent variables associated with overall survival using the six variables that were found to be significantly associated with overall survival in the univariate analysis.

PT: prothrombin time, DAA: direct-acting antiviral, SVR: sustained viral response, CI: confidence interval

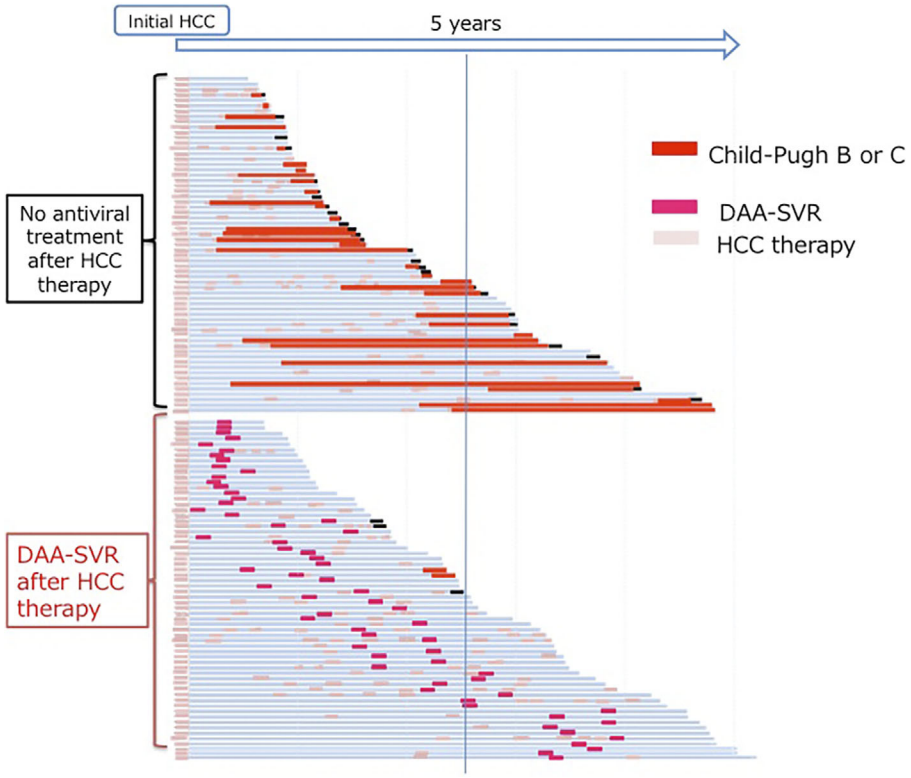

Figure 4. Changes in the Child-Pugh status in HCC patients of the DAA-SVR group and untreated group. Changes in the Child-Pugh status in HCC patients with and without DAA-SVR during the observation period are shown. HCC: hepatocellular carcinoma, DAA: direct-acting antiviral, SVR: sustained viral response

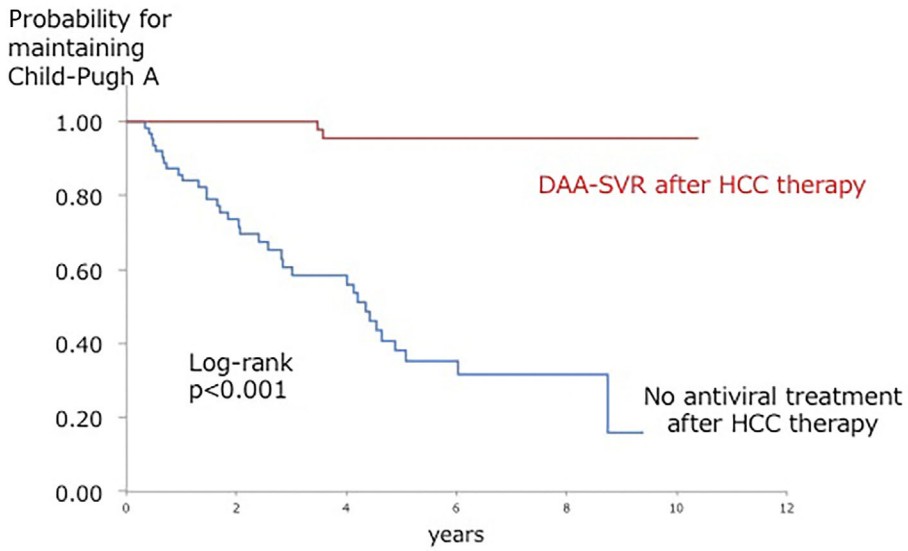

Figure 5. Probability of maintaining Child-Pugh A in patients of the DAA-SVR group and untreated group. The probability of maintaining Child-Pugh A among the 63 patients treated with DAAs (DAA-SVR after HCC therapy) and the 63 patients who did not receive DAAs (no antiviral treatment after HCC therapy) after propensity score matching is shown. The Kaplan-Meier method was used to assess the probability of maintaining Child-Pugh A, and the log-rank test was used for the comparison. HCC: hepatocellular carcinoma, DAA: direct-acting antiviral, SVR: sustained viral response

therapy is associated with an improvement in the liver function (37-40) as well as lower rates of hepatic decompensation (37, 38). These reports support the use of DAA therapy in patients with advanced liver disease and successfully treated HCC.

Reaching SVR12 is not an easy task in the HCC patient population. Only 69% of our population reached SVR12, a finding similar to the results of other retrospective analyses of DAA use in HCC patients (41, 42), compared to reported values of over 90% in populations powered to DAA efficacy (43). Part of this may be due to the difficulty of integrating HCV treatment into HCC care, as demonstrated by the low rate of HCC patients with HCV receiving DAA treatment. There is currently much debate about how aggressive clinicians should be in treating active HCV in HCC patients and whether or not DAA use reduces the recurrence rate of HCC (43-48). Recently, the American Gastroenterological Association (AGA) published a clinical practice update describing the interaction between DAA therapy for HCV and the HCC incidence, HCC recurrence, and DAA efficacy (49).

One limitation associated with our study is that we used patients' records from only one center in the cohort. To strengthen our findings further, we should conduct multi-institutional cohort study and analyze the OS of patients with HCV-related HCC with an SVR from DAAs compared with untreated controls. Whether or not aggressive anti-viral therapy for HCC patients with Child-Pugh B/C is beneficial should also be further studied.

In conclusion, patients with HCV-positive HCC achieving a DAA-SVR after HCC treatment showed a significantly better OS rate than HCV-untreated patients. The contribution of a DAA-SVR during the course of HCC treatment to a longer survival is mainly due to the prevention of the progression of Child-Pugh A to B/C.

All procedures followed have been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent was obtained from the patient for being included in the study.

The authors state that they have no Conflict of Interest (COI).

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