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Effect of direct-acting antivirals for hepatitis C virus-related hepatocellular carcinoma recurrence and death after curative treatment

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Background/Aim: There has been a long-standing debate about the association of direct-acting antiviral (DAA) therapy and hepatocellular carcinoma (HCC) recurrence. This study aimed to investigate the association between DAA therapy and HCC recurrence after curative therapy.

Methods: We retrospectively enrolled 1,021 patients with HCV-related (hepatitis C virus) HCC who underwent radiofrequency ablation (RFA), liver resection, or both as the first treatment modality from January 2007 to December 2016 and without a history of HCV therapy before HCC treatment from a nationwide database. The effect of HCV treatment on HCC recurrence and all-cause mortality was also investigated.

Results: Among the 1,021 patients, 77 (7.5%) were treated with DAA, 14 (1.4%) were treated with interferon-based therapy, and 930 (91.1%) did not receive HCV therapy. DAA therapy was an independent prognostic factor for lower HCC recurrence rate (hazard ratio [HR], 0.04; 95% confidence interval [CI], 0.006-0.289; *P*=0.001 for landmarks at 6 months after HCC treatment and HR, 0.05; 95% CI, 0.007-0.354; *P*=0.003 for landmarks at 1 year). Furthermore, DAA therapy was associated with lower all-cause mortality (HR, 0.049; 95% CI, 0.007-0.349; *P*=0.003 for landmarks at 6 months and HR, 0.063; 95% CI, 0.009-0.451; *P*=0.006 for landmarks at 1 year).

Conclusions: DAA therapy after curative HCC treatment can decrease HCC recurrence and all-cause mortality compared to interferon-based therapy or no antiviral therapy. Therefore, clinicians should consider administering DAA therapy after curative HCC treatment in patients with HCV-related HCC. **(J Liver Cancer 2022;22:125-135)**

Keywords: Carcinoma, hepatocellular; Antiviral agents; Risk factors; Hepatitis C, chronic; Recurrence

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INTRODUCTION

Since the introduction of direct-acting antiviral agents (DAAs) in the past decade, there has been remarkable development in the treatment of chronic hepatitis C. In the 2000s, a pegylated interferon (IFN)-based treatment regimen showed a virologic response of 40-70%. In the DAA era, the reported rate of sustained virologic response at 12 weeks is 90-98%, even in patients with advanced liver cirrhosis.[1-4] However, 71 million people are estimated to remain infected with hepatitis C virus (HCV). Chronic hepatitis C is considered a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC), especially in Western countries.[5,6] HCC is ranked the third most common cause of cancer-related deaths, and its incidence is expected to increase until 2030.[7]

Although there is no doubt that DAA therapy should be actively conducted to reduce the morbidity and mortality rate from HCC, whether DAA therapy should be applied to patients with HCV-related HCC is debated. Since the report of an unexpectedly high rate of early HCC recurrence in patients with HCV-related HCC after DAA therapy, several reports have made clinicians hesitant to recommend expensive DAA therapy to patients with HCC after curative treatment.[8] A study on Italian HCC cohorts reported that after curative treatment, patients had a high rate of HCC recurrence despite DAA therapy.[9] Another study conducted by Cabibbo et al.[10] showed that the risk of early HCC recurrence remained high after DAA therapy in patients who achieved complete remission (CR) of HCC. To date, few studies have demonstrated that DAA therapy has a significant beneficial effect in preventing HCC recurrence compared to the untreated or IFN-treated group.[11-13] Because of these contradictory results, patients with HCC may be excluded from DAA therapy even after CR is achieved.

In this context, our study aimed to elucidate the effect of DAA therapy on HCC recurrence risk by comparing patients who received DAA therapy with those who did not in a large-scale HCV-related HCC cohort provided by the Korea Health Insurance Review and Assessment (HIRA) database.

METHODS

1. Patient selection

We retrospectively reviewed patients with HCV-related HCC in the HIRA database. HIRA includes specific and detailed medical information on diagnosis, prescriptions, invasive procedures, surgeries, and sociodemographic data such as the age and sex of patients.[14] In South Korea, more than 98% of the total population is enrolled in the National Health Insurance.[14] Moreover, all medical institutions are required to practice under the supervision of National Health Insurance, which is based on reimbursement. A total of 2,283 subjects with HCV-related HCC (B18.2 and C22.0) who underwent radiofrequency ablation (RFA; Q7280, Q7281, and QZ841), liver resection (Q7221, Q7222, Q7223, Q7224, Q3051, Q3052, Q3053, Q3054, and Q3055), or both as the first treatment modality for HCC were extracted from the HIRA database using the International Classification of Disease (10th edition). The exclusion criteria were as follows: viral coinfection, including hepatitis B (B18.1, B18.10, B18.18, and Z22.5) and human immunodeficiency virus (B20.X, B21.X, B22.X, B23.X, and B24.X), autoimmune hepatitis (K75.4), Wilson's disease (E83.0), primary biliary cholangitis (K74.3, K74.30, K74.31, K74.32, and K74.39), primary sclerosing cholangitis (K83.0), alcoholic liver disease (K70.X), and history of antiviral therapy before or during HCC treat-

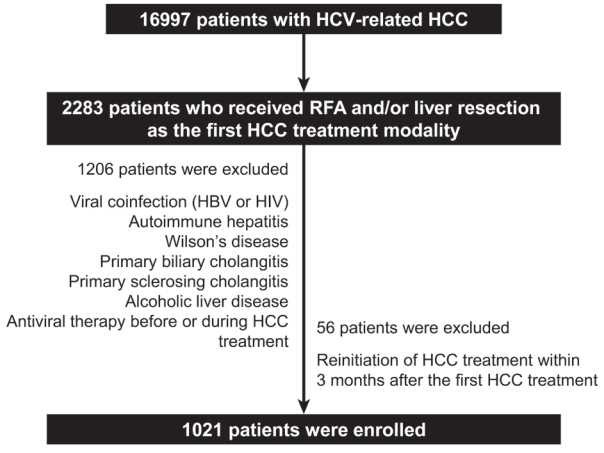

Figure 1. Flow diagram of patient enrollment. HCV, hepatitis C virus; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

ment. As radiologic findings were not available in the HIRA database, we excluded 56 patients who received another HCC treatment within 3 months after the first HCC treatment to enroll only patients who achieved complete response or sufficient HCC treatment with the first RFA or liver resection. We finally enlisted 1,021 patients (Fig. 1), who were followed up until death or until December 2016. The Institutional Review Board (IRB) of the Ajou University Hospital approved the study protocol (IRB No. AJIRB-MED-MDB-17-031). Patients were not required to provide informed consent because of the retrospective nature of the study and the use of fully de-identified data. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines were followed (Supplementary Table 1).

2. Definitions

Data on age, sex, liver cirrhosis (K74.X), diabetes (E11.X, E12.X, E13.X, and E14.X), the first HCC treatment modality, HCC treatment modality after recurrence, duration and regimen of antiviral therapy, and interval between HCC treatment and antiviral therapy were obtained. The antiviral treatment regimens investigated were DAA (638101ATB [daclatasvir], 638001ACH [asunaprevir], 644401ATB [sofosbuvir], 645800ATB [ledipasvir/sofosbuvir]), IFN (175502BIJ, 175503BIJ, 175504BIJ, 175530BIJ, 175601BIJ, 175602BIJ, 175630BIJ, 175631BIJ, 175801BIJ, 175901BIJ, 452602BIJ, 452630BIJ, 454830BIJ, and 454834BIJ), and ribavirin (223604ACH, 223601ACH, and 223601ACH). We assigned patients to the untreated group if HCC recurred before completion of DAA therapy. The primary outcome was HCC recurrence after the first treatment and the secondary outcome was all-cause mortality during follow-up. HCC recurrence was defined as reinitiation of HCC treatment 3 months after the first HCC treatment. The period from the first HCC treatment to HCC recurrence was regarded as the HCC recurrence time. Patients who underwent liver transplantation were treated for HCC recurrence and not censored. Death was defined as the medical outcome classification on the T200 table, and non-hospital deaths were excluded. Diabetes was diagnosed when diagnostic and medication codes were identified simultaneously.

3. Statistical analysis

All data management and analyses were performed using R statistical software (version 3.3.4; R Core Team [2014]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project. org/). A P-value <0.05 was considered statistically significant. Pearson's chi-square test or Fisher's exact test was used for categorical data; variables with an expected frequency of less than 5 were analyzed using the Fisher's exact test. Analysis of variance (ANOVA) was used to compare the groups for continuous data. Post-hoc comparisons after ANOVA were controlled using the Bonferroni correction. Factors associated with HCC recurrence or death were identified using the Cox proportional hazards model. In an analysis to ascertain the proportional hazard assumption of DAA and IFN-based treatments, the coefficients of time-dependent variables for treatment modality were identified as insignificant. Therefore, time-varying Cox analysis was not performed in this study.

We performed landmark analyses at 6 months and 1 year after the first HCC treatment to avoid immortal time bias. Landmark analysis is a suitable method to demonstrate time-to-event as a Kaplan-Meier curve.[15] Competing risk analysis was also conducted to correctly estimate the probabilities of HCC recurrence or death in the presence of competing events, such as death or HCC recurrence.[16]

The impact of treatment modality on HCC recurrence or all-cause mortality was identified through analysis between the DAA-treated and untreated cohorts and between the antiviral (DAA- or IFN-based)-treated and untreated cohorts.

RESULTS

1. Baseline characteristics of the HIRA cohort

A total of 1,021 patients with HCV-related HCC underwent RFA, liver resection, or both as the first treatment modality from January 2007 to December 2016 and did not receive antiviral therapy before HCC treatment. Among them, 77 patients had been treated with DAA therapy, 14 patients had received IFN therapy, and 930 patients did not undergo antiviral therapy after HCC treatment. The mean age and

proportion of male patients were 65.6±8.8 years and 44.1% in the DAA-treated group, 58.5±7.5 years and 78.6% in the IFN-treated group, 68.5±8.8 years and 57.7% in the untreated group, respectively. The numbers of patients diagnosed with liver cirrhosis and HCC recurrence were 55 (71.4%) and one (1.3%) in the DAA-treated group, eight (57.1%) and three (21.4%) in the IFN-treated group, and 667 (71.7%) and 507 (54.5%) in the untreated group, respectively. The number of patients who underwent liver resection and RFA was three (3.9%) and 74 (96.1%) in the DAA-treated group, two (14.3%) and 12 (85.7%) in the IFN-treated group, and 102 (11%) and 826 (88.8%) in the untreated group, respectively. Two patients in the untreated group underwent both planned liver resection and RFA during hospitalization. The median DAA therapy duration (interquartile range [IQR]) was 13.1 (8.3-18.7) weeks. Thirty-seven patients received DAA therapy for less than 12 weeks, and 40 patients received DAA therapy for 12-24 weeks. For the IFN-treated group, the median treatment duration (IQR) was 16.6 (5.3-42.6) weeks. Seven patients were treated for less

Table 1. Baseline characteristics of the study population: all patients

Variable	DAA-treated group (n=77)	IFN-treated group (n=14)	Untreated group (n=930)	*P*-value
Age (years)	65.6±8.8	58.5±7.5	68.5±8.8	<0.001*
Male gender	34 (41.2)	11 (78.6)	537 (57.7)	0.017*
Diabetes mellitus	35 (45.5)	7 (50.0)	341 (36.7)	0.193
Liver cirrhosis	55 (71.4)	8 (57.1)	667 (71.7)	0.457
HCC recurrence	1 (1.3)	3 (21.4)	507 (54.5)	<0.001*
HCC treatment modality				0.196
Resection	3 (3.9)	2 (14.3)	102 (11.0)	
RFA	74 (96.1)	12 (85.7)	826 (88.8)	
Resection+RFA			2 (0.2)	
DAA regimen				
Daclatasvir/asunaprevir	46 (59.7)			
Sofosbuvir/ribavirin	25 (32.5)			
Ledipasvir/sofosbuvir	6 (7.8)			
DAA regimen duration (weeks)	13.1 (8.3-18.7)			
<12	37 (48.1)			
12-24	40 (51.9)			
IFN regimen duration (weeks)		16.6 (5.3-42.6)		
<12		7 (50.0)		
12-24		5 (35.7)		
>24		2 (14.3)		
Interval between HCC treatment to antiviral therapy, months	14.3 (6.1-39.6)	16.1 (2.6-22.1)		
<3	12 (15.6)	4 (28.6)		
3-6	7 (9.1)	2 (14.3)		
6-12	15 (19.5)	2 (14.3)		
12-24	16 (20.7)	3 (21.4)		
>24	27 (35.1)	3 (21.4)		

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; DAA, direct acting antiviral agent; IFN, interferon.
*P<0.05.

than 12 weeks, five patients for 12-24 weeks, and two patients for more than 24 weeks. The interval between the first HCC treatment to antiviral therapy (IQR) was 14.3 (6.1-39.6) months in the DAA-treated group and 16.1 (2.6-22.1) months in the IFN-treated group (Table 1). The median follow-up period (IQR) was 684 (381-1,294) days in the DAA group, 1,583 (620-2,244) days in the IFN group, and 600 (304-1,163) days in the untreated group. Of the 199 patients who received their first HCC treatment after January 2015, 41 had been treated with DAA therapy, two received IFN therapy, and 156 did not undergo antiviral therapy after HCC treatment. The median follow-up period (IQR) was 394 (275-540) days in the DAA group, 400 (304-496) days in the IFN group, and 306 (148-478) days in the untreated group (Table 2).

2. Effect of DAA therapy and antiviral therapy on HCC recurrence

Using a multivariate Cox proportional hazard regression model, we investigated the impact of antiviral treatment modality on HCC recurrence by analyzing the DAA-treated and untreated cohorts and comparing antiviral (DAA- or IFN-based)-treated and untreated cohorts. The effects of age, sex, diabetes, cirrhosis, and first HCC treatment modality were adjusted for in this analysis. Compared with the untreated cohorts, the DAA-treated cohorts were independently associated with lower HCC recurrence (HR, 0.037; 95% CI, 0.005 to -0.261; $P<0.001$). In a landmark analysis at 6 months and

Table 2. Baseline characteristics of the study population: patients who received first HCC treatment after January 2015

Variable	DAA-treated group (n=41)	IFN-treated group (n=2)	Untreated group (n=156)	*P*-value
Age (years)	66.1±8.6	55.0±9.9	70.2±9.1	0.003*
Male gender	18 (43.9)	1 (50.0)	88 (56.4)	0.318
Diabetes mellitus	21 (51.2)	1 (50.0)	63 (40.4)	0.413
Liver cirrhosis	30 (73.2)	1 (50.0)	117 (75.0)	0.62
HCC recurrence	1 (2.4)	0 (0.0)	30 (19.2)	0.013*
HCC treatment modality				1
Resection			3 (1.9)	
RFA	41 (100.0)	2 (100.0)	153 (98.1)	
DAA regimen				
Daclatasvir/asunaprevir	24 (58.5)			
Sofosbuvir/ribavirin	12 (29.3)			
Ledipasvir/sofosbuvir	5 (12.2)			
DAA regimen duration (weeks)	16.1 (13.1-21.1)			
<12	14 (34.1)			
12-24	27 (65.9)			
IFN regimen duration (weeks)		10.3 (7.8-10.2)		
<12		2 (100.0)		
Interval between HCC treatment to antiviral therapy, months	6.4 (2.9-11.5)	6.1 (5.8-6.4)		
<3	12 (29.3)			
3-6	7 (17.1)	1 (50.0)		
6-12	13 (31.7)	1 (50.0)		
12-24	9 (21.9)			

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; DAA, direct acting antiviral agent; IFN, interferon.
*$P<0.05$.

1 year after the first HCC treatment, DAA-treated cohorts were consistently associated with lower HCC recurrence rates than untreated cohorts (HR, 0.04; 95% CI, 0.006-0.289; *P*=0.001; and HR, 0.05; 95% CI, 0.007-0.354; *P*=0.003, respectively). In an analysis of antiviral (DAA- or IFN-based)-treated and untreated cohorts, antiviral-treated cohorts were independently associated with lower HCC recurrence (HR, 0.086; 95% CI, 0.027-0.268; *P*<0.001). In a landmark analysis at 6 months and 1 year after the first HCC treatment, antiviral-treated cohorts were also consistently associated with lower HCC recurrence rates than untreated cohorts (HR, 0.094; 95% CI, 0.029-0.293; *P*<0.001; and HR, 0.111; 95% CI, 0.035-0.346, *P*<0.001, respectively) (Table 3).

Fig. 2A shows the cumulative probability of HCC recurrence estimated using the Kaplan-Meier method. The DAA-treated group showed lower probabilities of HCC recurrence than the IFN-treated and untreated groups (log-rank *P*=0.03, and log-rank *P*<0.001, respectively). The IFN-treated group was also associated with a lower probability of HCC recurrence than the untreated group (log-rank *P*=0.015). The cumulative HCC recurrence rates at 1, 2, and 5 years were 0%, 1.8%, and 1.8% in the DAA-treated group; 7.1%, 14.9%, and

Table 3. Univariate and multivariate analyses on the impact of antiviral treatment for CHC on HCC recurrence

Modality	Univariate Cox			Multivariate Cox*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
DAA vs. untreated	0.039	0.005-0.274	0.001†	0.037	0.005-0.261	<0.001†
DAA‡ vs. untreated	0.042	0.006-0.303	0.001†	0.040	0.006-0.289	0.001†
DAA§ vs. untreated	0.052	0.007-0.371	0.003†	0.050	0.007-0.354	0.003†
DAA or IFN vs. untreated	0.089	0.029-0.279	<0.001†	0.086	0.027-0.268	<0.001†
DAA or IFN‡ vs. untreated	0.098	0.032-0.307	<0.001†	0.094	0.029-0.293	<0.001†
DAA or IFN§ vs. untreated	0.117	0.038-0.368	<0.001†	0.111	0.035-0.346	<0.001†

HR, hazard ratio; CI, confidence interval; CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; DAA, direct acting antiviral agent; IFN, interferon.
*Adjusted for sex, age, diabetes, cirrhosis, first HCC treatment modality; †*P*<0.05; ‡Landmark analysis at 6 months after first HCC treatment; §Landmark analysis at 1 year after first HCC treatment.

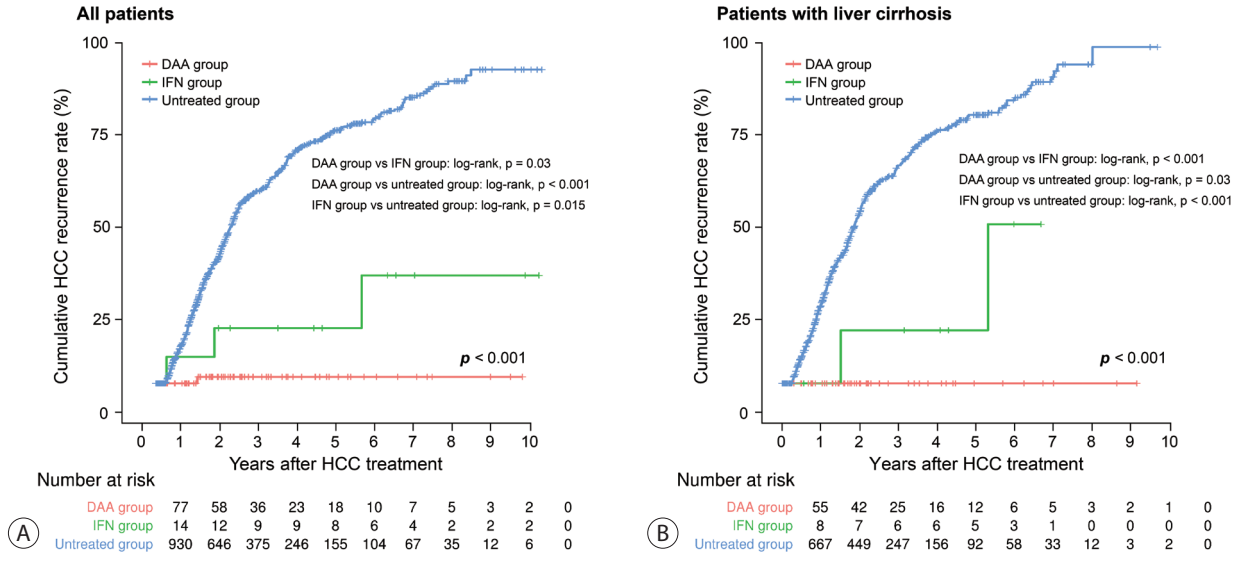

Figure 2. Cumulative incidence of HCC recurrence using the Kaplan-Meier analysis in all patients (A) and patients with liver cirrhosis (B). DAA, direct acting antivirals; IFN, interferon; HCC, hepatocellular carcinoma.

14.9% in the IFN-treated group; and 19.7%, 43.6%, and 69.3% in the untreated group, respectively (P<0.001). Among patients with cirrhosis, those who underwent DAA therapy showed lower probabilities of HCC recurrence than the IFN-treated and untreated cohorts (log rank P<0.001 and log rank P=0.03, respectively). The IFN-treated group was also associated with a lower probability of HCC recurrence than the untreated group (log-rank P<0.001). The probabilities of HCC recurrence at 1, 2, and 5 years were 0.0%, 14.3%, and 14.3%, respectively, in the IFN-treated group and 20.7%, 46.1%, and 72.3%, respectively, in the untreated group. In the DAA-treated group, none of the patients with cirrhosis experienced HCC recurrence (P<0.001) (Fig. 2B).

Supplementary Tables 2, 3 show the effects of other variables on HCC recurrence. According to univariate Cox regression analysis, liver cirrhosis was a significant predictor of HCC recurrence. However, age, sex, diabetes, and first HCC treatment modality, including RFA and surgical resection, were not related to HCC recurrence. Supplementary Tables 4, 5 show the treatment modalities used after the HCC recurrence.

3. Impact of DAA therapy and antiviral therapy on all-cause mortality

We investigated independent factors for all-cause mortality by analyzing the DAA-treated and untreated cohorts and comparing antiviral (DAA- or IFN-based)-treated and untreated cohorts (Table 4). Multivariate regression with the Cox model was adjusted for age, sex, diabetes, cirrhosis, and first HCC treatment modality. DAA-treated cohorts were associated with lower mortality than untreated cohorts (HR, 0.044; 95% CI, 0.006-0.313; P=0.002). In a landmark analysis at 6 months and 1 year after the first HCC treatment, DAA-treated cohorts were associated with lower all-cause mortality than untreated cohorts (HR, 0.049; 95% CI, 0.007-0.349; P=0.003; and HR, 0.063; 95% CI, 0.009-0.451; P=0.006, respectively). In an analysis of antiviral (DAA- or IFN-based)-treated and untreated cohorts, antiviral-treated cohorts were associated with lower all-cause mortality (hazard ratio [HR], 0.066; 95% confidence interval [CI], 0.016-0.266; P<0.001). In a landmark analysis at 6 months and 1 year after the first HCC treatment, antiviral therapy was also consistently associated with lower all-cause mortality than in the untreated cohorts (HR, 0.037; 95% CI, 0.005-0.263; P<0.001; and HR, 0.047; 95% CI, 0.007-0.334; P=0.002, respectively).

DISCUSSION

The aim of the present study was to demonstrate the benefits or harms of DAA therapy on HCC recurrence after curative therapy in Korean patients. Our study elucidated that DAA therapy is associated with lower HCC recurrence and all-cause mortality than IFN-based therapy or no treatment in patients with HCV-related HCC after curative therapy.

Since Reig et al.[8] reported an unexpectedly high rate of early HCC recurrence in patients with HCV-related HCC af-

Table 4. Univariate and multivariate analyses on the impact of antiviral treatment for CHC on death

Modality	Univariate Cox			Multivariate Cox*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
DAA vs. untreated	0.042	0.006-0.297	0.002†	0.044	0.006-0.313	0.002†
DAA‡ vs. untreated	0.047	0.007-0.336	0.002†	0.049	0.007-0.349	0.003†
DAA§ vs. untreated	0.060	0.008-0.427	0.004†	0.063	0.009-0.451	0.006†
DAA or IFN vs. untreated	0.060	0.015-0.243	<0.001†	0.066	0.016-0.266	<0.001†
DAA or IFN‡ vs. untreated	0.034	0.005-0.241	<0.001†	0.037	0.005-0.263	<0.001†
DAA or IFN§ vs. untreated	0.042	0.006-0.300	0.002†	0.047	0.007-0.334	0.002†

HR, hazard ratio; CI, confidence interval; CHC, chronic hepatitis C; DAA, direct acting antiviral agent; IFN, interferon.
*Adjusted for sex, age, diabetes, cirrhosis, first HCC treatment modality; †P<0.05; ‡Landmark analysis at 6 months after first HCC treatment; §Landmark analysis at 1 year after first HCC treatment.

ter DAA therapy, many studies have been conducted to refute this observation. Most studies have concluded that DAA therapy does not increase the HCC recurrence rate. However, a serious concern regarding these results is that they amplify rather than resolve suspicions regarding the efficacy of DAA therapy. The findings indicated that DAA therapy did not increase or decrease HCC recurrence. In a study on French ANRS CO22 HEPATHER cohorts, including 189 patients who underwent DAA therapy and 78 patients who did not receive antiviral therapy, the HCC recurrence rates were 0.73/100 person-months and 0.66/100 person-months in the DAA-treated and untreated groups, respectively (P=0.8756).[17] Singal et al.[18] also demonstrated that DAA therapy was not related to increased or decreased HCC recurrence rate using landmark analysis at 90 days (HR, 0.92; 95% CI, 0.60-1.41), 120 days (HR, 0.99; 95% CI, 0.66-1.48), and 6 months (HR, 0.98; 95% CI, 0.69-1.40) from CR. Another study showed that the cumulative probabilities of HCC recurrence-free survival at 1 and 2 years were 85.1% and 73.2% in the DAA-treated group and 82.9% and 78.2% in the untreated group (P=0.278), respectively.[19] Moreover, some studies have suggested that DAA therapy is inferior to IFN therapy in the inhibition of HCC recurrence. IFN-based treatment has previously been shown to be effective for recurrence-free survival.[20-22] In 2020, Kuo et al.[23] reported that the DAA-treated group showed poor HCC recurrence-free survival compared to the IFN-treated group (75.4% vs. 95.0%, P<0.001). Another study demonstrated that the tertiary prevention effect on HCC recurrence was invalid in DAA therapy but was durable in IFN-based therapy.[24] Most of the authors who insisted that DAA therapy increases HCC recurrence or that DAA therapy is inferior to IFN therapy for secondary prevention of HCC present immunological hypotheses. In 2015, Serti et al.[25] reported that DAA-induced rapid HCV clearance was related to a decline in intrahepatic immune function mediated by IFN and natural killer cell activation. It has been hypothesized that these immune-mediated inhibitory effects on HCC cell proliferation change after DAA therapy. These changes are also associated with HCC recurrence.[21] In contrast, Minami et al.[12] reported that DAA therapy was not inferior to IFN treatment for the prevention of early HCC recurrence (HR, 0.65; P=0.28). Nagata et al.[11] also revealed that the early HCC recurrence risk was similar between the IFN-treated and DAA-treated groups (P=0.54). A meta-regression conducted by Waziry et al.[26] also showed that DAA therapy was not related to higher HCC recurrence than IFN treatment (adjusted rate ratio, 0.62; 95% CI, 0.11-3.45; P=0.56).

An ostensible consensus on DAA therapy and HCC recurrence seems to have already been reached. However, there has been an active debate over this controversial topic. In 2018, the European Association for the Study of the Liver guidelines also stated that it is unclear whether DAA therapy increases the HCC recurrence rate and suggested close surveillance in these patients.[27] According to the 2018 American Association for the Study of Liver Diseases guidelines for HCC management, the impact of DAA therapy on the potential risk of HCC recurrence is uncertain and requires further investigation.[28] As no medical provider will prescribe medications without a therapeutic effect, it is necessary to continue to prove through further research that DAA therapy is at least equivalent to IFN-based therapy and superior to the untreated group in inhibiting HCC recurrence.

Although studies on DAA therapy-related HCC recurrence have been actively conducted worldwide, large-scale population-based investigations in Korean cohorts have not been conducted. In the present study, we included over 1,000 Korean patients with an acceptable follow-up period. Our study, which included patients without antiviral therapy as a control group, demonstrated that DAA therapy is an independent protective factor against HCC recurrence and all-cause mortality in patients with HCV-related HCC after curative treatment. In addition, Kaplan-Meier analysis using the log-rank test with Bonferroni corrections showed that DAA therapy is more effective in preventing HCC recurrence than IFN-based therapy.

Our study had several limitations. First, the limited number of study subjects in the IFN and DAA groups did not allow for a definite conclusion within this study. Furthermore, approximately 50% of the IFN-treated group received insufficient treatment duration, and the effect of IFN treatment on HCC recurrence could not be adequately reflected. Sec-

ond, because data were extracted from HIRA, the results of imaging studies and laboratory findings such as alpha-fetoprotein, total bilirubin, international normalized ratio, and albumin were not available. Thus, the detailed tumor burden, underlying liver function, and CR acquisition status based on radiologic findings could not be identified. Furthermore, we could not perform PS matching because of data limitations. Third, because HCC recurrence was defined according to the reinitiation of HCC treatment, patients who stopped treatment when HCC recurred after the first treatment may have been misclassified as the non-recurrence group. We struggled to establish inclusion criteria because of these limitations. We are convinced that these controversies have been overcome by including only those patients who received RFA or underwent liver resection as an initial HCC treatment and did not undergo any other treatment within 3 months. Fourth, we only presented the results from landmark analysis as a table, not a figure. This can be misleading to the readers. However, we presented Kaplan-Meier curves because the group variable did not violate the assumption with testing by the Schoenfeld residuals tests (IFN group rho=-0.0302. chisq=0.467, P=0.494/DAA group rho=-0.0267, chisq=0.365, P=0.546).[29]

In conclusion, DAA therapy was not associated with an increase in the HCC recurrence rate after RFA or liver resection but was associated with a significantly lower HCC recurrence rate than the untreated group. Therefore, clinicians should consider administering DAA therapy after curative HCC treatment in patients with HCV-related HCC.

Conflict of Interest

The authors have no conflicts to disclose.

Ethics Statement

Patients were not required to provide informed consent because of the retrospective nature of the study and the use of fully de-identified data. The Institutional Review Board (IRB) of the Ajou University Hospital approved the study protocol (IRB No. AJIRB-MED-MDB-17-031).

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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Supplementary Material

Supplementary data can be found with this article online https://doi.org/10.17998/jlc.2022.05.24.

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Supplementary Table 5. Management of HCC recurrence: patients who received first HCC treatment after January 2015

Treatment of HCC recurrence	DAA treated group (n=1)	Untreated group (n=30)
RFA	1	29
Liver transplantation		1

HCC, hepatocellular carcinoma; DAA, direct acting antiviral age.