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Observational Study

Hepatocellular carcinoma, decompensation, and mortality based on hepatitis C treatment: A prospective cohort study

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Abstract

BACKGROUND

Prospective studies of the long-term outcomes of patients with hepatitis C virus (HCV) infection after treatment with interferon-based therapy (IBT) or direct-acting antivirals (DAA) are limited in many Asian countries.

AIM

To elucidate the incidences of hepatocellular carcinoma (HCC) and

death/transplantation based on treatment with IBT or DAA, to compare the outcomes of the sustained virologic response (SVR) to IBT and DAA, and to investigate outcome-determining factors after SVR.

METHODS

This cohort included 2054 viremic patients (mean age, 57 years; 46.5% male; 27.4% with cirrhosis) prospectively enrolled at seven hospitals between 2007 and 2019. They were classified as the untreated group (n = 619), IBT group (n = 578), and DAA group (n = 857). Outcomes included the incidences of HCC and death/transplantation. The incidences of the outcomes for each group according to treatment were calculated using an exact method based on the Poisson distribution. A multivariate Cox regression analysis was performed to determine the factors associated with HCC or death/transplantation, followed by propensity score matching to confirm the results.

RESULTS

During a median of 4.1 years of follow-up, HCC and death/transplantation occurred in 113 and 206 patients, respectively, in the entire cohort. Compared with the untreated group, the incidences of HCC and death/transplantation were significantly lower in the IBT group [adjusted hazard ratio (aHR) 0.47, 95%CI: 0.28-0.80 and aHR 0.28, 95%CI: 0.18-0.43, respectively] and the DAA group (aHR 0.58, 95%CI: 0.35-0.96, and aHR 0.19, 95%CI: 0.20-0.68, respectively). Among 1268 patients who attained SVR with IBT (n = 451) or DAA (n = 816), the multivariable-adjusted analysis showed no differences in the risks of HCC (HR 2.03; 95%CI: 0.76-5.43) and death/transplantation (HR 1.38; 95%CI: 0.55-3.49) between the two groups. This was confirmed by a propensity score-matching analysis. Independent factors for HCC after SVR were age, genotype 1, and the presence of cirrhosis.

CONCLUSION

Treatment and achieving SVR with either IBT or DAA significantly reduced the incidences of HCC and mortality in the Asian patients with HCV infection. The risks of HCC and mortality were not significantly different regardless of whether SVR was induced by IBT or DAA.

Key Words: Hepatitis C virus; Direct-acting antiviral; Sustained virologic response; Hepatocellular carcinoma; Mortality

Core Tip: Treatment and sustained virologic response (SVR) with either interferon-based treatment (IBT) or direct-acting antiviral (DAA) significantly reduced the incidences of hepatocellular carcinoma and mortality in our Asian prospective cohort. The risks of HCC and all-cause of mortality were not significantly different regardless of whether SVR was induced by IBT or DAA. After achieving SVR, age, the presence of cirrhosis, and genotype 1 hepatitis C virus infection were indicators of worse clinical outcomes.

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INTRODUCTION

Hepatitis C virus (HCV) is a major cause of liver cirrhosis, hepatocellular carcinoma (HCC), and liver-related and overall mortality. In 2019, the World Health Organization estimated that 58 million people worldwide had chronic HCV infection[1]. Currently, this substantial public health burden can be reduced by active screening and treatment with highly tolerable direct-acting antivirals (DAA), which result in a cure rate of more than 95% in terms of the sustained virologic response (SVR)[2-4].

From the identification of HCV to the introduction of DAA therapy, interferon (IFN)-based therapy (IBT) was the only option for HCV treatment, with an approximate SVR rate of 50%[5]. Although IBT-induced SVR includes a wide variety of adverse effects and narrow indications, it significantly reduces the incidence of HCC and long-term mortality[6,7]. Furthermore, DAA-induced SVR has resulted in

reductions in hepatic fibrosis[8,9], portal hypertension[10], hepatic decompensation[11], HCC incidence [11,12], and liver-related and overall mortality[11,13]; however, the follow-up durations were relatively short.

To reach the HCV elimination goal of 2030, it is imperative to understand the regional epidemiology and outcomes of HCV. However, prospective studies of the long-term outcomes after treatment with IBT or DAA are limited in many Asian countries, where hepatitis B virus (HBV) is the major cause of liver-related complications. Additionally, comparative studies of the outcomes of SVR induced by IBT and DAA are scarce.

We established a prospective, nationwide, multicenter HCV cohort (the Korea HCV cohort study) funded by the Korean National Institute of Health in 2007. Using these data, we aimed to elucidate the clinical outcomes, including HCC, hepatic decompensation, and all-cause death, among Korean patients with chronic HCV infection. We compared the outcomes based on the antiviral treatments (untreated, IBT, and DAA) and analyzed patients after achieving SVR (IBT-SVR and DAA-SVR groups). Additionally, we investigated outcome-determining factors after SVR.

MATERIALS AND METHODS

Study subjects

The Korea HCV cohort is a prospective cohort of 2485 adult patients with HCV RNA positivity at seven tertiary centers nationwide enrolled from January 2007 to June 2019 in South Korea. Patients who met any of the following criteria were excluded: Positive serology for HBV surface antigen (n = 62) or HIV (n = 2); decompensated cirrhosis at enrollment (n = 79); previous antiviral treatment before cohort entry (n = 260); and less than 6 mo of follow-up (n = 28). Additionally, patients who had HCC before or at the time of cohort entry were excluded.

Therefore, 2054 viremic patients with or without compensated cirrhosis were analyzed as the entire cohort, which was further classified into three groups based on their treatment: untreated group (n = 619; 30.2%); IBT group (n = 578; 28.1%); and DAA group (n = 857; 41.7%). Patients in the untreated group did not receive IBT or DAA treatment during the entire follow-up period. Subject selection, classification, and overall outcomes are summarized in Figure 1.

In the entire cohort, 1267 patients achieved SVR (61.7%) with IBT (n = 451) or DAA (n = 816); these patients comprised the SVR cohort. Diagnostic criteria for liver cirrhosis were based on histology or at least one clinical sign of portal hypertension, such as cirrhotic features on radiological images, platelet count less than 100,000/mm^3, and documented gastroesophageal varices without hemorrhage. The study protocol was approved by the Institutional Review Board of seven hospitals, and each enrolled patient provided written informed consent.

Data collection at baseline and follow-up visits

At the time of enrollment, trained research coordinators at the seven hospitals interviewed the patients using a standardized questionnaire that included demographic and socioeconomic factors (age, sex, body mass index, education level, and occupation), health behaviors (smoking and alcohol consumption), comorbidities (extrahepatic cancers, thyroid disease, psychiatric disease, diabetes, kidney disease, cerebrovascular disease, and cardiovascular disease), and lifetime exposure to risk factors for HCV infection.

Laboratory data at baseline and follow-up visits were collected from the medical records, including the anti-HCV antibody, serum HCV RNA level, HCV genotype, HBV surface antigen, HBV core antibody immunoglobulin G (anti-HBc IgG), white blood cell count, hemoglobin, platelet count, aspartate aminotransferasel (AST), alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, creatinine, prothrombin time (PT) and alpha-fetoprotein (AFP). The following three non-invasive serum fibrosis assessment scores were calculated at the index date: The fibrosis-4 (FIB-4) index [14], the AST-to-platelet ratio index (APRI) score[15], and the albumin-bilirubin (ALBI) score[16].

The results of imaging studies, such as abdominal ultrasonography or computed tomography, liver pathology, and transient elastography (FibroScan®, Echosens, Paris, France), were collected when available. Detailed information about antiviral treatment, including therapeutic regimens, duration, and achievement of SVR, was collected from the patients' medical records. These data were entered into the established electronic case report form on the authorized website of the Korean Centers for Disease Control Korea HCV cohort study (http://is.cdc.go.kr/) by the research coordinators. All input data were quality-controlled by independent statistical researchers (Baik D, Choi HY, and Ki M) at least four times per year.

Follow-up evaluations

All patients underwent regular clinical assessments every 3 to 12 mo, and HCV treatment was recommended by their attending physicians according to the treatment guidelines for HCV infection unless there were contraindications or patient's refusal. If the patients were treated, then SVR was evaluated, and regular follow-up visits every 6 to 12 mo after SVR were encouraged. HCC surveillance

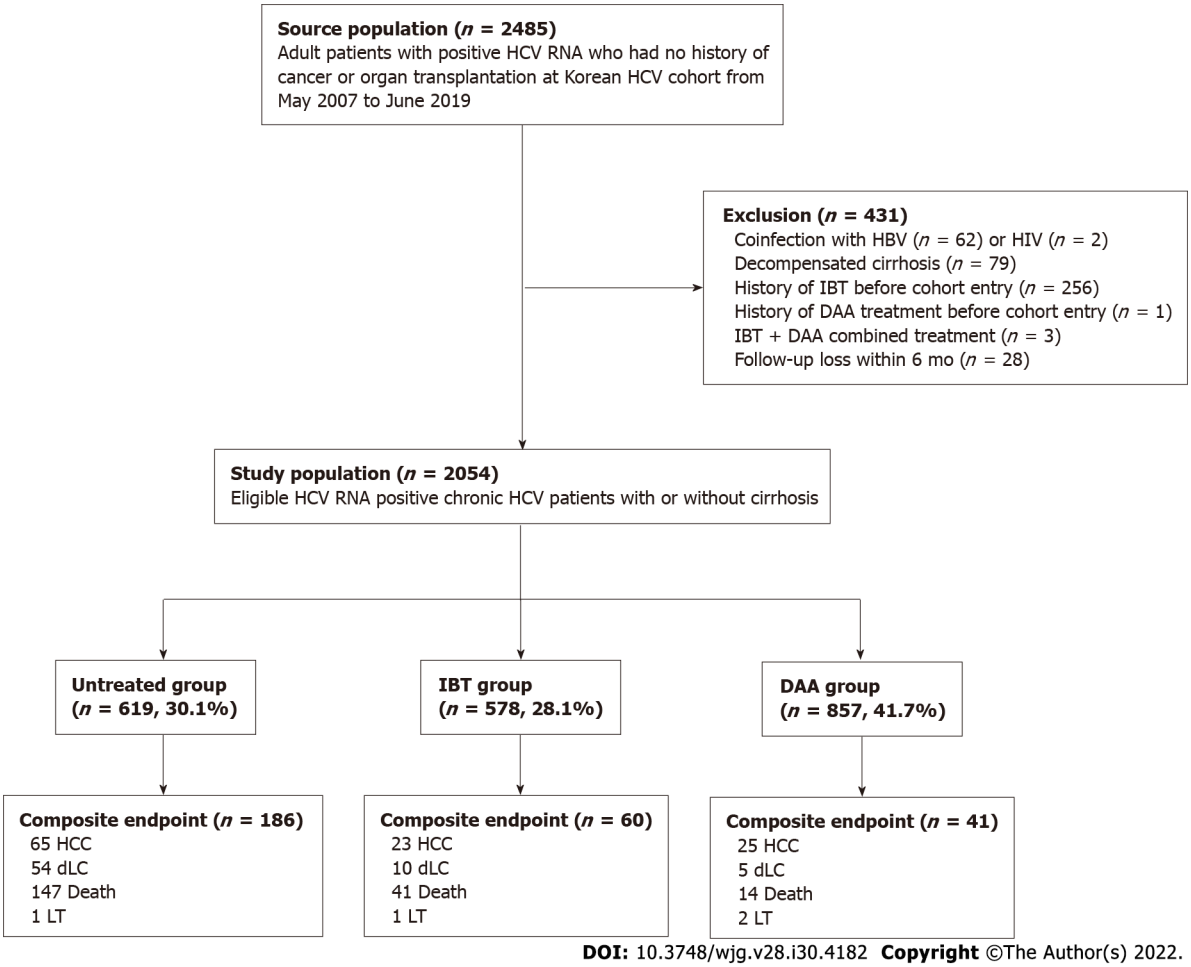

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Figure 1 Patient flow diagram. DAA: Direct-acting antivirals; dLC: Decompensated liver cirrhosis; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; IBT: Interferon-based treatment; HIV: Human immunodeficiency virus; LT: Liver transplantation.

using abdominal ultrasonography and serum AFP tests every 6 to 12 mo were recommended according to the pretreatment fibrosis stage. If the patients did not adhere to the regular follow-up schedule, then research coordinators called the patients or their families to encourage them to attend the clinic and to check their survival status, disease progression to hepatic decompensation, or development of HCC. The end of follow-up was defined as the date of death/liver transplantation (LT), or the last follow-up date (June 30, 2020).

Measurement of liver-related outcomes

Outcomes included the incidences of HCC, hepatic decompensation, and death/LT. HCC was diagnosed according to pathology or typical imaging criteria observed on dynamic computed tomography and/or magnetic resonance imaging in accordance with the Korean Liver Cancer Study Group guidelines (similar to major international guidelines)[17]. Decompensated liver cirrhosis was defined as the presence of ascites, jaundice, variceal bleeding, encephalopathy, or a combination of these [18]. All-cause mortality or death/LT was directly documented or indirectly indicated as disqualification from the National Health Insurance status provided in the electronic medical records. In Korea, enrollment in the National Health Insurance is compulsory for all individuals; therefore, disqualification from the National Health Insurance indicates death or emigration in most cases[19]. To verify the survival status, physician-confirmed death certificate data, including the date and cause of death, were obtained from the Statistics Korea mortality database, which was established in 1981.

To calculate the outcomes of the entire cohort, the index date of the entire cohort was defined as the date of cohort entry when HCV RNA positivity was confirmed by the referred clinics. To compare the outcomes of patients with SVR induced by IBT and patients with SVR induced by DAA, the index date for the SVR cohort was defined as the initiation day of the antiviral treatment. SVR was evaluated using an intention-to-treat analysis; therefore, patients who received at least one dose of IBT or DAA were included.

Statistical analysis

Baseline characteristics of the patients were compared using the chi-square test for categorical variables, and a one-way analysis of variance (ANOVA) or *t*-test was used for continuous variables. For multiple comparisons, a one-way ANOVA was used followed by a Bonferroni correction. The total follow-up (in person-years) of each group was calculated by multiplying the cohort population size by the average follow-up in years. Survival time was calculated as the time from cohort entry (the entire cohort) or the start of the first treatment (SVR cohort) until the date of death/LT or the last available follow-up date. A few patients who received a second course of DAA treatment because of failure of the first DAA treatment were censored at the time of retreatment.

The incidences and 95% confidence intervals (CI) of the outcomes for each group based on treatment were calculated using an exact method based on the Poisson distribution. Cumulative incidence curves for outcome development were estimated using the pseudo-Kaplan–Meier method with a clock reset procedure for patients treated with IBT or DAA during follow-up and compared using the log-rank test. Therefore, patients who had received IBT and subsequent DAA treatment were considered as the DAA group, but the period between IBT and DAA treatment was included in the IBT group with no event.

A time-varying Cox regression model was used to determine the factors associated with outcomes, and the adjusted hazard ratio was estimated for the entire cohort and the SVR cohort. In the models, baseline variables (sex, body mass index, alcohol, smoking, HCV genotype) were adjusted, and age, antiviral treatment, laboratory data, achievement of SVR, and presence of cirrhosis were considered time-dependent variables. A multivariate Cox regression analysis was performed to determine the factors associated with HCC or death/LT, and the adjusted hazard ratio was estimated for the SVR cohort at the time of IBT or DAA initiation. Covariates with $P < 0.05$ in the univariate Cox regression model were used as covariates for the multivariate Cox regression analyses. To confirm the multivariate analysis results for the SVR cohort, significant differences in characteristics at the time of initiation of each treatment were adjusted by propensity score (PS) matching for all possible variables, including the time from cohort entry to treatment. We used nearest-neighbor matching with a caliper size of 0.1 and matched the patients using a 1:1 ratio. The covariate balance was considered to be achieved if the absolute standardized difference between the two groups was ≤ 0.1.

All *P*-values were two-sided, and $P < 0.05$ was considered significant. SPSS (version 21; IBC Corp., Armonk, NY, United States) and R (version 4.0.4; http://cran.r-project.org/) software were used for statistical analyses. The R package of *MatchIt* was used for matching analyses.

RESULTS

Baseline characteristics of the entire cohort

The demographic, clinical, and laboratory characteristics of the entire cohort ($n = 2054$), untreated group ($n = 619$; 30.1%), IBT group ($n = 578$; 28.1%), and DAA group ($n = 857$; 41.7%) at the index date are provided in Table 1. The mean age of the patients was 57 years; 46.5% were men and 27.4% had compensated cirrhosis.

Compared with the untreated and DAA groups, the IBT group was significantly younger, had a higher proportion of genotype 2, lower rates of alcohol consumption, cirrhosis and high FIB-4 index values (≥ 3.25), and fewer comorbidities.

Among the DAA group, 14.0% had been treated with an IFN-based regimen after cohort enrollment, and 86.0% were treatment-naive. DAA treatments administered were sofosbuvir plus ribavirin (32.1%), daclatasvir plus asunaprevir (26.3%), elbasvir plus grazoprevir (13.7%), glecaprevir plus pibrentasvir (13.7%), ledipasvir plus sofosbuvir (9.1%), and ombitasvir plus paritaprevir plus ritonavir plus dasabuvir (3.9%).

Incidences of HCC, decompensation, and death/LT in the entire cohort according to treatment, SVR, or the presence of liver cirrhosis

The median time periods between cohort entry (index date) and the end of follow-up were 5.6 years [interquartile range (IQR), 3.4-8.2] for the untreated group, 7.9 years (IQR, 6.1-9.7) for the IBT group, and 3.5 years (IQR, 2.0-5.5) for the DAA group (Table 1). During this period, 113 patients developed HCC, 69 patients experienced hepatic decompensation, 202 patients died (119 Liver related and 83 non-liver related), and four patients underwent LT.

As shown in Table 2, the estimated HCC incidence rates per 100 person-years for the untreated group, IBT group, and DAA group were 1.98 (95%CI: 1.56-2.52), 0.59 (95%CI: 0.39-0.89), and 1.16 (95%CI: 0.78-1.71), respectively (Table 2). The incidence rates of hepatic decompensation per 100 person-years for the untreated group, IBT group, and DAA group were 1.62 (95%CI: 1.24-2.11), 0.25 (95%CI: 0.14-0.47), and 0.23 (95%CI: 0.10-0.55), respectively. The incidence rates of death/LT per 100 person-years for the untreated group, IBT group, and DAA group were 3.33 (95%CI: 2.85-3.91), 0.87 (95%CI: 0.64-1.18), and 0.65 (95%CI: 0.40-1.06), respectively. The incidence rates of all three outcomes were significantly lower in the IBT and DAA groups compared with the untreated group. However, the

Table 1 Baseline characteristics of the entire hepatitis C virus cohort according to the treatment

Variable, *n* (%)	Untreated group (*n* = 619)	IBT group (*n* = 578)	DAA group (*n* = 857)	*P* value (3 Gr.)	*P* value (U *vs* I)	*P* value (U *vs* D)	*P* value (I *vs* D)
Age (yr)	60.4 ± 13.4	51.4 ± 10.9	59.1±11.4	< 0.001	< 0.001	0.086	< 0.001
Male sex	280 (45.2)	277 (47.9)	412 (48.1)	0.511	0.351	0.281	0.955
HCV RNA, $\log_{10}$ IU/mL	5.89 (5.08-6.45)	5.83 (4.87-6.49)	6.04 (5.27-6.53)	< 0.001	0.979	0.017	< 0.001
HCV genotype				< 0.001	< 0.001	< 0.001	< 0.001
1	256 (41.4)	242 (41.9)	491 (57.3)				
2	299 (48.3)	323 (55.9)	355 (41.4)				
Others/missing	64 (10.3)	13 (2.2)	11 (1.3)				
Diagnosis status				< 0.001	< 0.001	0.002	0.058
Chronic hepatitis	417 (67.4)	456 (78.9)	639 (74.6)				
Compensated cirrhosis	202 (32.6)	122 (21.1)	218 (25.4)				
FIB-4 index				< 0.001	< 0.001	0.142	< 0.001
≤ 1.45	112 (18.9)	191 (33.3)	164 (19.9)				
1.45-3.25	218 (36.8)	200 (34.8)	337 (40.9)				
≥ 3.25	263 (44.3)	183 (31.9)	323 (39.2)				
APRI score				0.15	0.09	0.094	0.853
≤ 2.0	480 (80.3)	485 (84.1)	708 (83.7)				
> 2.0	118 (19.7)	92 (15.9)	138 (16.3)				
ALBI score				0.004	0.04	0.001	0.313
≤ -2.60 (Grade 1)	446 (73.0)	450 (78.1)	674 (80.3)				
> -2.60 (Grade 2 or 3)	165 (27.0)	126 (21.9)	165 (19.7)				
Ever smoker	264 (42.9)	283 (49.5)	380 (44.5)	0.058	0.022	0.519	0.068
Alcohol intake				< 0.001	< 0.001	< 0.001	< 0.001
None	326 (53.0)	226 (39.4)	419 (48.9)				
Social	227 (36.9)	308 (53.7)	229 (26.7)				
Significant[1]	61 (9.9)	40 (7.0)	209 (24.4)				
Fatty liver disease on imaging study, *n* = 1389	71 (19.3), *n* = 367	86 (21.1), *n* = 408	140 (22.8), *n* = 614	0.435	0.549	0.202	0.516
Anti-HBcIgG (+), *n* = 1442	47 (11.0), *n* = 429	33 (8.4), *n* = 391	64 (10.3), *n* = 622	0.46	0.225	0.73	0.33
BMI, kg/m^2	23.4 ± 3.2	23.8 ± 3.0	23.8 ± 3.1	0.02	0.143	0.02	1
Diabetes mellitus	120 (19.4)	77 (13.3)	128 (14.9)	0.01	0.005	0.024	0.391
Hypertension	145 (23.4)	107 (18.5)	243 (28.4)	< 0.001	0.037	0.034	< 0.001
Cardiovascular disease	16 (2.6)	3 (0.5)	25 (2.9)	0.006	0.004	0.701	0.001
Cerebrovascular disease	17 (2.7)	4 (0.7)	20 (2.3)	0.026	0.007	0.617	0.017
Laboratory study							
WBC, × 10^3/mm^3	5.09 (4.29-6.50)	5.05 (3.91-6.16)	5.40 (4.40-6.61)	< 0.001	0.145	0.164	< 0.001
Hemoglobin, g/dL	13.5 (12.3-14.5)	13.7 (12.7-14.8)	13.8 (12.7-14.8)	< 0.001	0.004	< 0.001	1
Platelet, × 10^3/mm^3	162 (118-212)	174 (130-220)	172 (129-215)	0.229	0.236	0.317	1
Albumin, g/dL	4.2 (3.9-4.4)	4.2 (4.0-4.5)	4.2 (4.0-4.4)	< 0.001	< 0.001	0.001	1
Total bilirubin, mg/dL	0.8 (0.5-1.0)	0.7 (0.6-1.0)	0.7 (0.6-1.0)	0.784	1	1	1
ALP, IU/L	87 (68-136)	79 (63-112)	121 (78-250)	< 0.001	0.001	< 0.001	< 0.001

AST, IU/L	50 (30-85)	50 (31-83)	46 (30-76)	0.026	1	0.139	0.038
ALT, IU/L	42 (23-80)	52 (29-100)	36 (22-70)	< 0.001	0.013	0.176	< 0.001
Creatinine, mg/dL	0.9 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.857	1	1	1
PT, INR	1.06 (1.01-1.12)	1.03 (0.98-1.08)	1.03 (0.97-1.09)	< 0.001	< 0.001	0.007	0.119
AFP, ng/dL	4.3 (2.5-9.7)	3.5 (2.3-7.1)	3.8 (2.4-6.6)	0.868	1	1	1
Cohort entry time				< 0.001	< 0.001	< 0.001	< 0.001
January 2007–June 2015	488 (78.8)	561 (97.1)	49 (5.7)				
July 2015–June 2019	131 (21.2)	17 (2.9)	808 (94.3)				
SVR rate	-	67.5 (451/668)	95.3 (817/857)	-	-	< 0.001	-
Follow-up duration (yr)	5.6 (3.4-8.2)	7.9 (6.1-9.7)	3.5 (2.0-5.5)	< 0.001	< 0.001	< 0.001	< 0.001

[1]Significant alcohol intake is defined as weekly ≥ 210 g for men and ≥ 140 g for women.

Data were presented as mean ± SD, median (interquartile range), or *n* (%). AFP: Alpha-feto protein; ALBI: Albumin-bilirubin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APRI: Aspartate aminotransferase to platelet ratio index; AST: Aspartate aminotransferase; BMI: Body mass index; DAA: Direct acting antivirals; FIB-4: Fibrosis-4; HCV: Hepatitis C virus; IBT: Interferon-based therapy; INR: International normalized ratio; PT: Prothrombin time; WBC: White blood cell.

incidence of HCC in the non-cirrhotic group was not significantly different between the untreated and DAA groups, while the incidences of decompensation and death/LT were significantly lower in the DAA group compared with the untreated group. The cumulative outcome incidences for the untreated, IBT, and DAA groups are shown in Figure 2, and those for the non-cirrhotic and cirrhotic subgroups are shown in Supplementary Figures 1 and 2, respectively.

Multivariable analyses of factors associated with HCC, decompensation, and death/LT in the entire cohort

A multivariable time-varying Cox regression analysis with the untreated group as a reference showed that IBT [hazard ratio (HR), 0.47; 95%CI: 0.28-0.80; $P = 0.005$] and DAA groups (HR, 0.58; 95%CI: 0.35-0.96; $P = 0.035$) were independently associated with a significantly lower risk of HCC (Table 3, model 1). Other independent HCC risk factors were older age (HR, 1.06; 95%CI: 1.03-1.08; $P < 0.001$), male sex (HR, 2.50; 95%CI: 1.37-4.55; $P = 0.003$), genotype 1 (HR, 2.25; 95%CI: 1.45-3.48; $P < 0.001$), the presence of cirrhosis (HR, 3.81; 95%CI: 2.38-6.10; $P < 0.001$), significant alcohol consumption (HR, 2.20; 95%CI: 1.14-4.24; $P = 0.027$), prolonged PT (HR, 2.66; 95%CI: 1.13-6.24; $P = 0.025$), and higher AFP level (HR, 2.12; 95%CI: 1.48-3.05; $P < 0.001$) (Table 3, model 1).

The death/LT incidence decreased independently after antiviral treatment with IBT (HR, 0.28; 95%CI: 0.19-0.43; $P < 0.001$) or DAA (HR, 0.19; 95%CI: 0.10-0.35; $P < 0.001$) (Table 3, model 1). In contrast, older age (HR, 1.05; 95%CI: 1.03-1.06; $P < 0.001$), male sex (HR, 1.70; 95%CI: 1.24-2.33; $P < 0.001$), the presence of cirrhosis (HR, 1.88; 95%CI: 1.34-2.64; $P < 0.001$), lower body mass index (HR, 0.94; 95%CI: 0.89-0.99; $P = 0.019$), lower albumin level (HR, 0.35; 95%CI: 0.25-0.51; $P < 0.001$), and prolonged PT (HR, 2.34; 95%CI: 1.06-5.16; $P = 0.034$) independently increased mortality/LT rates. Antiviral treatment, cirrhosis, albumin level, and PT were independently associated with the risk of decompensation (Table 3, model 1).

We established another multivariable model (model 2) by replacing the achievement of SVR instead of IBT or DAA treatment. A multivariate time-varying Cox regression analysis of the combined outcomes of the untreated and no SVR groups as a reference showed that SVR induced by either IBT or DAA significantly decreased the risk of HCC (HR, 0.41; 95%CI: 0.26-0.65; $P < 0.001$), decompensation (HR, 0.10; 95%CI: 0.04-0.29; $P < 0.001$), and death/LT (HR, 0.26; 95%CI: 0.17-0.39; $P < 0.001$) (Table 3, model 2).

Comparison of the clinical outcomes of the IBT-SVR group and DAA-SVR group in the SVR cohort: Unadjusted and PS-matched results

The SVR cohort comprised 1,268 chronic HCV patients who achieved SVR with IBT or DAA (IBT-SVR group, $n = 451$; DAA-SVR group, $n = 817$). The SVR rates of the IBT and DAA groups were 67.5% and 95.3%, respectively. The baseline characteristics at the time of initiation of treatment of the IBT and DAA groups according to SVR are shown in Supplementary Table 1. The incidence rates of HCC, decompensation, and death/LT were significantly lower in the IBT-SVR group than in the IBT-no SVR group (Supplementary Table 2). In contrast, the incidence rate of death/LT was significantly lower in the DAA-SVR group than in the DAA-no SVR group, whereas the incidence rates of HCC and decompensation did not reach statistical significance, probably because of the short follow-up or rare incidence of decompensation (Supplementary Table 2).

Table 2 Annual incidence rates of hepatocellular carcinoma, decompensation and death/transplantation according to treatment exposure and the presence of cirrhosis

	Group	PY	No. of events	No./100 PY (95%CI)	HR (95%CI)	*P* value
Entire cohort	Hepatocellular carcinoma					
	Untreated group	3285.4	65	1.98 (1.56-2.52)	Reference	-
	IBT group	3888.9	23	0.59 (0.39-0.89)	0.31 (0.19-0.49)	< 0.001
	DAA group	2158.0	25	1.16 (0.78-1.71)	0.59 (0.37-0.95)	0.029
	Decompensation					
	Untreated group	3333.6	54	1.62 (1.24-2.11)	Reference	-
	IBT group	3950.1	10	0.25 (0.14-0.47)	0.15 (0.07-0.29)	< 0.001
	DAA group	2178.7	5	0.23 (0.10-0.55)	0.16 (0.06-0.39)	< 0.001
	Death or transplantation					
	Untreated group	4438.3	148	3.33 (2.85-3.91)	Reference	-
	IBT group	4850.1	42	0.87 (0.64-1.18)	0.22 (0.16-0.31)	< 0.001
	DAA group	2467.2	16	0.65 (0.40-1.06)	0.30 (0.17-0.51)	< 0.001
No cirrhosis	Hepatocellular carcinoma					
	Untreated group	2364.6	15	0.63 (0.38-1.05)	Reference	-
	IBT group	2971.8	6	0.20 (0.09-0.45)	0.30 (0.11-0.77)	0.012
	DAA group	1569.4	8	0.51 (0.26-1.02)	0.90 (0.37-2.18)	0.812
	Decompensation					
	Untreated group	2369.9	6	0.25 (0.11-0.56)	Reference	-
	IBT group	2992.3	1	0.03 (0.00-0.24)	0.09 (0.01-0.74)	0.026
	DAA group	1573.4	0	0.00	0.00	N/A
	Death or transplantation					
	Untreated group	3176.3	63	1.98 (4.15-7.12)	Reference	-
	IBT group	3712.3	22	0.59 (0.39-0.90)	0.26 (0.16-0.42)	< 0.001
	DAA group	1784.6	7	0.39 (0.19-0.82)	0.33 (0.15-0.75)	0.008
Cirrhosis	Hepatocellular carcinoma					
	Untreated group	919.9	50	5.44 (4.15-7.12)	Reference	-
	IBT group	917.1	17	1.85 (1.16-2.97)	0.35 (0.20-0.61)	< 0.001
	DAA group	588.6	17	2.89 (1.81-4.61)	0.53 (0.30-0.92)	0.025
	Decompensation					
	Untreated group	962.8	48	4.99 (3.78-6.57)	Reference	-
	IBT group	957.7	9	0.84 (0.49-1.80)	0.18 (0.09-0.37)	< 0.001
	DAA group	606.3	5	0.82 (0.34-1.97)	0.17 (0.07-0.44)	< 0.001
	Death or transplantation					
	Untreated group	1262.1	85	6.73 (5.48-8.27)	Reference	-
	IBT group	1137.8	20	1.76 (1.14-2.71)	0.21 (0.13-0.35)	< 0.001
	DAA group	682.6	9	1.32 (0.69-2.52)	0.28 (0.14-0.56)	< 0.001

A Cox proportional hazards model was used to determine hazards ratios and *P* values. CI: Confidence interval; DAA: Direct acting antivirals; HR: Hazard ratio; IBT: Interferon-based therapy; N/A: Not applicable; PY: Person-year.

Table 3 Multivariate time-varying Cox regression analysis for hepatocellular carcinoma and death/transplantation in entire cohort

Variable	Hepatocellular carcinoma		Decompensation		Death/transplantation	
	aHR (95%CI)	*P* value	aHR (95%CI)	*P* value	aHR (95%CI)	*P* value
Model 1						
Untreated group	Reference	-	Reference	-	Reference	-
IBT group	0.47 (0.28-0.80)	0.005	0.16 (0.08-0.33)	< 0.001	0.28 (0.18-0.43)	< 0.001
DAA group	0.58 (0.35-0.96)	0.035	0.12 (0.03-0.33)	< 0.001	0.19 (0.10-0.35)	< 0.001
Age, yr	1.06 (1.03-1.08)	< 0.001	1.00 (0.98-1.03)	0.805	1.05 (1.03-1.06)	< 0.001
Male sex	2.50 (1.37-4.55)	0.003	-	-	1.70 (1.24-2.33)	< 0.001
HCV genotype			-	-	-	-
2	Reference	-				
1	2.25 (1.45-3.48)	< 0.001				
Others/unknown	1.72 (0.66-4.48)	0.266				
Cirrhosis	3.81 (2.38-6.10)	< 0.001	9.26 (4.03-21.03)	< 0.001	1.88 (1.34-2.64)	< 0.001
Ever smoker	1.47 (0.82-2.66)	0.192	-	-	-	-
Alcohol consumption			-	-	-	-
None	Reference	-				
Social	1.20 (0.73-1.98)	0.473				
Significant	2.20 (1.14-4.24)	0.027				
BMI, kg/m^2	-	-	-	-	0.94 (0.89-0.99)	0.019
Diabetes mellitus	0.96 (0.59-1.56)	0.872	-	-	1.12 (0.77-1.62)	0.563
Albumin, g/dL	0.71 (0.44-1.15)	0.162	0.35 (0.20-0.63)	< 0.001	0.36 (0.25-0.51)	< 0.001
Total bilirubin, mg/dL	0.95 (0.80-1.12)	0.568	1.03 (0.98-1.08)	0.264	-	-
PT, INR	2.66 (1.13-6.24)	0.025	3.32 (1.08-10.19)	0.036	2.34 (1.06-5.16)	0.034
AFP, $\log_{10}$ ng/dL	2.12 (1.48-3.05)	< 0.001	1.54 (0.95-2.51)	0.08	1.29 (0.94-1.77)	0.112
Model 2						
Untreated or no SVR	Reference	-	Reference	-	Reference	-
SVR	0.41 (0.26-0.65)	< 0.001	0.10 (0.04-0.29)	< 0.001	0.26 (0.17-0.39)	< 0.001
Age, yr	1.06 (1.04- 1.08)	< 0.001	1.02 (0.99-1.04)	0.152	1.06 (1.04-1.07)	< 0.001
Male sex	2.50 (1.38-4.54)	0.003	-	-	1.68 (1.23-2.30)	0.001
HCV genotype			-	-	-	-
2	Reference	-				
1	2.25 (1.45-3.48)	< 0.001				
Others/unknown	1.57 (0.60-4.09)	0.359				
Cirrhosis	3.75 (2.35-6.01)	< 0.001	7.54 (3.32-17.15)	< 0.001	1.72 (1.23-2.41)	0.002
Ever smoker	1.53 (0.85-2.75)	0.156	-	-	-	-
Alcohol consumption			-	-	-	-
None	Reference	-				
Social	1.24 (0.75-2.04)	0.397				
Significant	2.69 (1.40-5.16)	0.003				
BMI, kg/m^2	-	-	-	-	0.94 (0.89-0.99)	0.024
Diabetes mellitus	0.99 (0.61-1.61)	0.959	-	-	1.10 (0.76-1.60)	0.612
Albumin, g/dL	0.76 (0.47-1.20)	0.238	0.42 (0.24-0.71)	0.001	0.42 (0.30-0.60)	< 0.001

Total bilirubin, mg/dL	0.96 (0.81-1.13)	0.624	1.03 (0.99-1.08)	0.156	-	-
PT, INR	2.53 (1.02-6.28)	0.044	4.42 (1.48-13.20)	0.008	2.69 (1.22-5.92)	0.014
AFP, $\log_{10}$ ng/dL	2.10 (1.46-3.02)	< 0.001	1.48 (0.90-2.44)	0.12	1.17 (0.86-1.60)	0.32

Total number of patients, 2197; number of hepatocellular carcinomas, 113; number of deaths, 202; number of transplantations, 4; number of decompensations, 69. AFP: Alpha-feto protein; aHR: Adjusted hazard ratio; BMI: Body mass index; CI: Confidence interval; DAA: Direct acting antivirals; HCV: Hepatitis C virus; IBT: Interferon-based therapy; PT: Prothrombin time; SVR: Sustained virologic response.

In the SVR cohort (5880.4 patient-years), 30 patients developed HCC, 6 patients had decompensation, 35 patients died, and no patient underwent LT during follow-up. The cumulative incidence rates of HCC at 2 and 5 years were 0.6% and 1.6%, respectively for non-cirrhotic patients with SVR (n = 985), and 4.8% and 10.1%, respectively, for cirrhotic SVR patients (n = 283). The cumulative HCC risk according to the presence of cirrhosis, FIB-4 index, APRI score, and ALBI score were significantly different (Supplementary Figure 3). However, HBcIgG positivity (HR, 0.39; 95%CI: 0.05-2.89; P = 0.358) and the presence of fatty liver disease (HR, 0.16; 95%CI: 0.02-1.18; P = 0.072) were not significant risk factors for the development HCC.

Comparisons of the clinical characteristics and outcomes of the IBT-SVR and DAA-SVR groups before and after PS matching (Table 4) yielded 213 matched pairs of patients from the IBT-SVR and DAA-SVR groups with no significant between-group differences in all baseline variables. Before PS matching, the DAA-SVR group had a significantly higher risk of HCC than the IBT-SVR group (HR, 3.53; 95%CI: 1.47-8.49; P = 0.005) (Supplementary Figure 4A), whereas the risks of decompensation (HR, 2.45; 95%CI: 0.33-18.37; P = 0.382) and death/LT (HR, 1.44; 95%CI: 0.62-3.34; P = 0.400) did not reach statistical significance (Supplementary Figure 4B and C). However, after PS matching, the DAA-SVR group showed no significant differences in the risks of HCC (HR, 2.72; 95%CI: 0.63-11.81; P = 0.179), decompensation (HR, 9.74; 95%CI: 0.42-224.81; P = 0.155), and death/LT (HR, 2.18; 95%CI: 0.47-10.15; P = 0.318) compared with the IBT-SVR group (Figure 3).

Multivariable-adjusted analyses of factors associated with outcomes of the SVR cohort

According to the multivariable-adjusted analysis, the DAA-SVR group did not show any independent differences in the development of HCC (HR, 2.03; 95%CI: 0.76-5.43; P = 0.160) or death/LT (HR, 1.38; 95%CI: 0.55-3.49; P = 0.494) compared with the IBT-SVR group (Table 5). Covariates independently associated with a higher incidence of HCC were older age (HR, 1.05; 95%CI: 1.01-1.10; P = 0.025), genotype 1 (HR, 3.02; 95%CI: 1.18-7.68; P = 0.021), and the presence of cirrhosis (HR, 3.18; 95%CI: 1.33-7.68; P = 0.009) after adjustment for the antiviral treatment regimen, sex, alcohol consumption, diabetes mellitus, albumin level, PT, and AFP level (Table 5). Additionally, covariates independently associated with death/LT risk were the presence of cirrhosis (HR, 2.97; 95%CI: 1.42-6.20; P = 0.004) and PT (HR, 5.27; 95%CI: 1.01-27.53; P = 0.049).

DISCUSSION

We analyzed the incidence rates of HCC, decompensation, and all-cause death/LT in a large, prospective, Asian cohort including 2054 patients with chronic HCV infection. During a median follow-up period of 4.1 years, the risks of HCC, decompensation, and all-cause mortality were significantly lower after treatment with IBT or DAA compared with no treatment.

After statistical adjustment, including a time-varying Cox analysis and PS-matched analysis, the risks of HCC, decompensation, and all-cause mortality were not significantly different regardless of whether SVR was achieved after IBT or DAA treatment; however, the follow-up duration of the DAA group was shorter than that of the IBT group. After achieving SVR, independent factors associated with HCC risk were no treatment, age, male sex, HCV genotype 1, cirrhosis, alcohol consumption, PT, and pretreatment AFP level, whereas independent factors associated with all-cause mortality were cirrhosis and PT.

There are limited studies of the association between antiviral treatment (IBT or DAA) and all-cause mortality, especially those involving Asian cohorts. Many studies focused on liver-related mortality rather than all-cause mortality as the primary outcome after SVR achievement. However, extrahepatic mortality should be considered for patients with HCV because HCV is associated with increased cardiovascular disease events[20] and extrahepatic malignancies such as bile duct cancers and diffuse large B-cell lymphoma[21,22]. Moreover, Tada *et al*[23] reported that IBT could reduce all-cause mortality and HCC risk even in patients who did not achieve SVR. However, the effect of DAA treatment in the absence of SVR on clinical outcomes is unknown. Therefore, this study focused on the effect of treatment on the outcomes including all-cause mortality in the entire cohort, and the effect of SVR induced by IBT and DDA on the outcomes in the SVR cohort.

Table 4 Comparison of characteristics and outcomes between the interferon-based treatment-sustained virologic response and direct-acting antivirals-sustained virologic response groups: Unadjusted and propensity score matching groups

Variable	Before adjustment				PS matched			
	IBT-SVR group (*n* = 451)	DAA-SVR group (*n* = 817)	*P* value	SMD	IBT-SVR group (*n* = 213)	DAA-SVR group (*n* = 213)	*P* value	SMD
Age, yr	51.0 ± 10.6	59.1 ± 11.4	< 0.001	0.741	53.9 ± 9.8	53.7 ± 11.4	0.823	0.022
Male sex	209 (46.3)	394 (48.2)	0.52	0.036	102 (47.9)	97 (45.5)	0.627	0.047
HCV RNA, $xlog_{10}$ IU/mL	5.72 (4.77-6.37)	6.04 (5.26-6.52)	< 0.001	0.278	5.84 (4.91-6.53)	6.07 (5.21-6.50)	0.439	0.073
HCV genotype			< 0.001	0.406			0.731	0.058
1	167 (37.0)	464 (56.8)			95 (44.6)	101 (47.4)		
2	278 (61.6)	342 (41.9)			116 (54.5)	111 (52.1)		
Others	6 (1.3)	11 (1.3)			2 (0.9)	1 (0.5)		
Entry-to-treat, year	0 (0-0.3)	0.2 (0-2.1)	< 0.001	0.654	0.1 (0-0.4)	0.1 (0-0.4)	0.78	0.125
Diagnosis status			0.001	0.192			0.901	0.012
Chronic hepatitis	373 (82.7)	612 (74.9)			174 (81.7)	173 (81.2)		
Compensated cirrhosis	78 (17.3)	205 (25.1)			39 (18.3)	40 (18.8)		
FIB-4 index			< 0.001	0.294			0.363	0.071
≤ 1.45	156 (34.8)	156 (19.9)			69 (32.7)	59 (29.1)		
1.45–3.25	155 (34.6)	326 (41.6)			74 (35.1)	85 (41.9)		
≥ 3.25	137 (30.6)	302 (38.5)			68 (32.2)	59 (29.1)		
APRI score			0.562	0.096			0.108	0.048
< 2.0	383 (85.1)	676 (83.9)			186 (87.7)	170 (82.1)		
≥ 2.0	67 (14.9)	130 (16.1)			26 (12.3)	37 (17.9)		
ALBI score			0.958	0.044			0.339	0.054
≤ -2.60 (Grade 1)	360 (80.0)	639 (79.9)			172 (81.1)	172 (82.7)		
> -2.60 (Grade 2 or 3)	90 (20.0)	161 (20.1)			40 (18.9)	36 (16.3)		
Ever smoker	228 (50.8)	15 (37.5)	0.045	0.162	95 (44.6)	93 (43.7)	0.527	0.019
Alcohol intake			< 0.001	0.669			0.816	0.058
None	171 (38.0)	19 (47.5)			98 (46.0)	104 (48.8)		
Social	245 (54.4)	13 (32.5)			88 (41.3)	85 (39.9)		
Significant[1]	34 (7.6)	8 (20.0)			27 (12.7)	24 (11.3)		
Fatty liver disease on imaging study	77 (22.8), *n* = 337	131 (22.4), *n* = 586	0.863	0.039	34 (24.3)	35 (24.8)	0.917	0.013
Anti-HBc IgG positivity	25 (8.6), *n* = 290	62 (10.5), *n* = 592	0.386	0.062	12 (7.8)	15 (9.7)	0.546	0.062
BMI, kg/m^2	23.7 ± 3.0	23.9 ± 3.1	0.429	0.047	23.9 ± 2.9	23.9 ± 3.4	0.983	0.005
Diabetes mellitus	61 (13.6)	122 (14.9)	0.495	0.049	26 (12.2)	22 (10.3)	0.54	0.055
Hypertension	80 (17.7)	236 (28.9)	< 0.001	0.267	45 (21.1)	44 (20.7)	0.905	0.012
Cardiovascular disease	3 (0.7)	24 (2.9)	0.007	0.162	2 (0.9)	3 (1.4)	0.315	0.058
Cerebrovascular disease	2 (0.4)	19 (2.3)	0.012	0.172	1 (0.5)	3 (1.4)	0.315	0.141
Laboratory study								
WBC, $\times 10^3/mm^3$	4.99 (3.90-6.10)	5.40 (4.40-6.63)	< 0.0010.297	0.24	5.26 (4.25-6.35)	5.35 (4.50-6.52)	0.787	0.027
Hemoglobin, g/dL	13.6 (12.6-14.9)	13.8 (12.8-14.8)	0.218	0.061	13.9 (12.8-14.9)	13.9 (12.8-14.9)	0.916	0.01

PLT, × 10^3/mm^3	177 (136-220)	173 (130-216)	0.178	0.055	176 (136-222)	180 (139-219)	0.401	0.083
Albumin, g/dL	4.2 (4.0-4.5)	4.2 (4.0-4.4)	0.664	0.082	4.3 (4.0-4.5)	4.3 (4.0-4.5)	0.734	0.031
Total bilirubin, mg/dL	0.7 (0.6-1.0)	0.7 (0.6-1.0)	< 0.001	0.072	0.8 (0.6-1.0)	0.7 (0.6-1.0)	0.85	0.009
ALP, IU/L	80 (63-113)	122 (78-250)	0.012	0.612	90 (65-126)	96 (72-183)	0.524	0.072
AST, IU/L	50 (30-86)	46 (30-76)	< 0.001	0.156	50 (32-83)	42 (27-85)	0.899	0.012
ALT, IU/L	54 (29-105)	36 (22-70)	0.756	0.297	49 (29-85)	37 (21-91)	0.915	0.009
Creatinine, mg/dL	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.02	0.09	0.8 (0.7-1.0)	0.8 (0.7-0.9)	0.176	0.069
PT, INR	1.03 (0.98-1.08)	1.04 (0.99-1.10)	0.434	0.111	1.03 (0.98-1.08)	1.04 (0.87-1.09)	0.67	0.038
AFP, ng/dL	3.3 (2.3-6.3)	3.8 (2.3-6.5)		0.142	5.8 (4.9-6.5)	6.1 (5.2-6.5)	0.278	0.034

[1]Significant alcohol intake is defined as weekly alcohol consumption ≥ 210 g for men and ≥ 140 g for women.
Data were presented as mean ± SD, median (interquartile range), or *n* (%). AFP: Alpha-feto protein; ALBI: Albumin-bilirubin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APRI: Aspartate aminotransferase to platelet ratio index; AST: Aspartate aminotransferase; BMI: Body mass index; DAA: Direct acting antivirals; FIB-4: Fibrosis-4; HCV: Hepatitis C virus; IBT: Interferon-based therapy; MELD: Model for end-stage liver disease; PLT: Platelet; PT: Prothrombin time; WBC: White blood cell; SVR: Sustained virologic response.

Table 5 Multivariate Cox regression analysis for hepatocellular carcinoma and death/transplantation among the sustained virologic response cohort

Variable	Hepatocellular carcinoma		Death/transplantation	
	aHR (95%CI)	*P* value	aHR (95%CI)	*P* value
IBT-SVR group	Reference	-	Reference	-
DAA-SVR group	2.03 (0.76-5.43)	0.16	1.38 (0.55-3.49)	0.494
Age, yr	1.05 (1.01-1.10)	0.025	-	-
Male sex	2.89 (0.97-8.61)	0.057	-	-
HCV genotype			-	–
2	Reference	-		
1	3.02 (1.18-7.68)	0.021		
Cirrhosis	3.18 (1.33-7.68)	0.009	2.97 (1.42-6.20)	0.004
Ever smoker	0.72 (0.26-1.99)	0.545	-	-
Alcohol consumption			-	-
None	Reference	-		
Social	2.62 (0.92-7.60)	0.072		
Significant	2.51 (0.71-8.82)	0.152		
BMI, kg/m^2	-	-	-	-
Diabetes mellitus	1.03 (0.42-2.52)	0.952	2.16 (0.98-4.78)	0.057
Albumin, g/dL	0.53 (0.19-1.49)	0.228	-	-
Total bilirubin, mg/dL	-	-	-	-
PT, INR	4.12 (0.89-19.17)	0.071	5.27 (1.01-27.53)	0.049
AFP, log_{10} ng/dL	1.07 (0.49-2.34)	0.858	-	-

Total number of patients, 1250; number of hepatocellular carcinomas, 30; number of deaths, 7; number of transplantations, 3. AFP: Alpha-feto protein; aHR: Adjusted hazard ratio; BMI: Body mass index; CI: Confidence interval; DAA: Direct acting antivirals; HCV: Hepatitis C virus; IBT: Interferon-based therapy; PT: Prothrombin time; SVR: Sustained virologic response.

Recent 5-year follow-up studies after DAA treatment showed that SVR is associated with a gradual but significant reduction in liver fibrosis in terms of FIB-4, METAVIR, transient elastography, and Child-Pugh score[24,25], whereas another study showed that induced SVR was associated with a reduced risk of clinical disease progression in patients with Child-Pugh A cirrhosis but not in patients

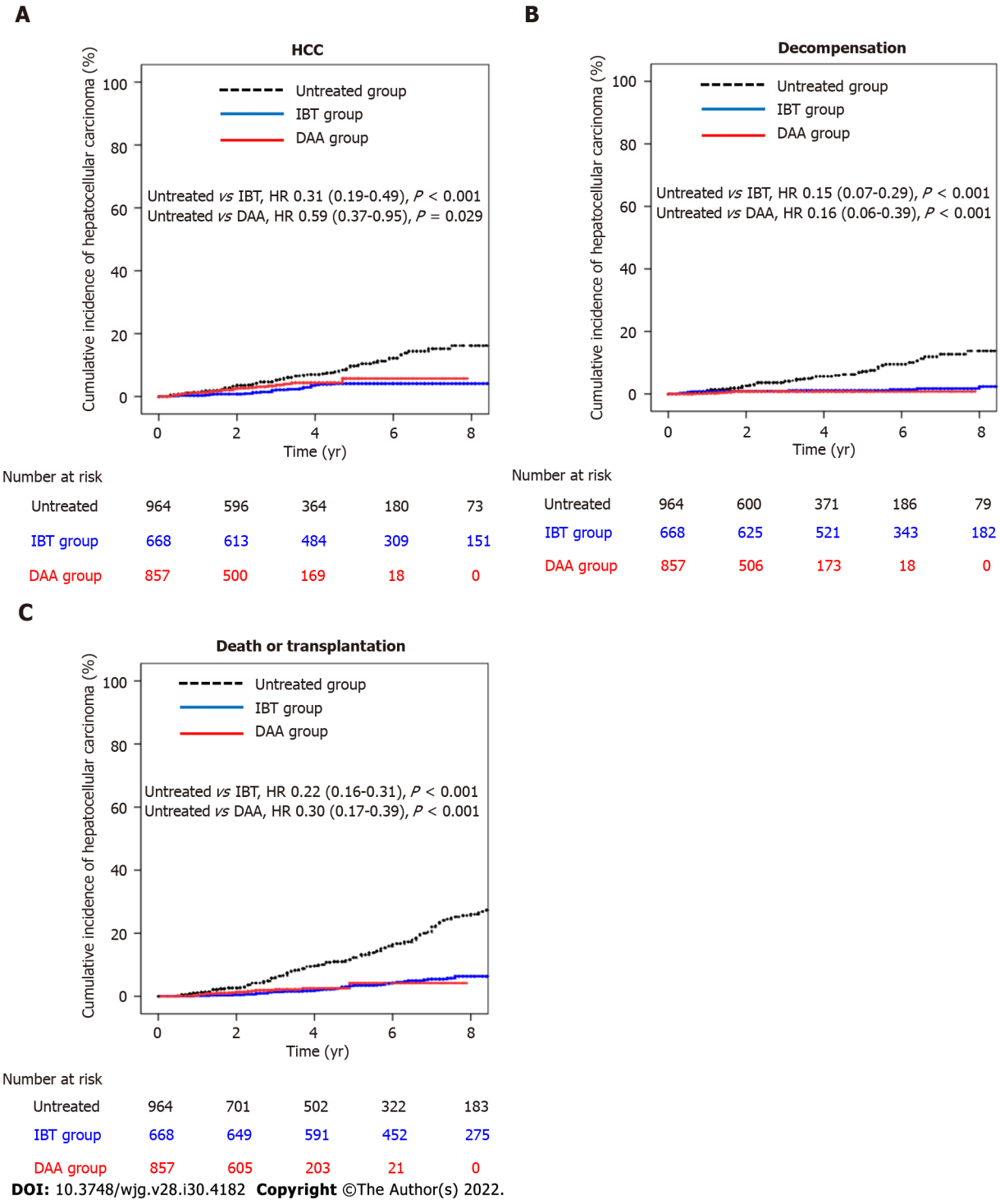

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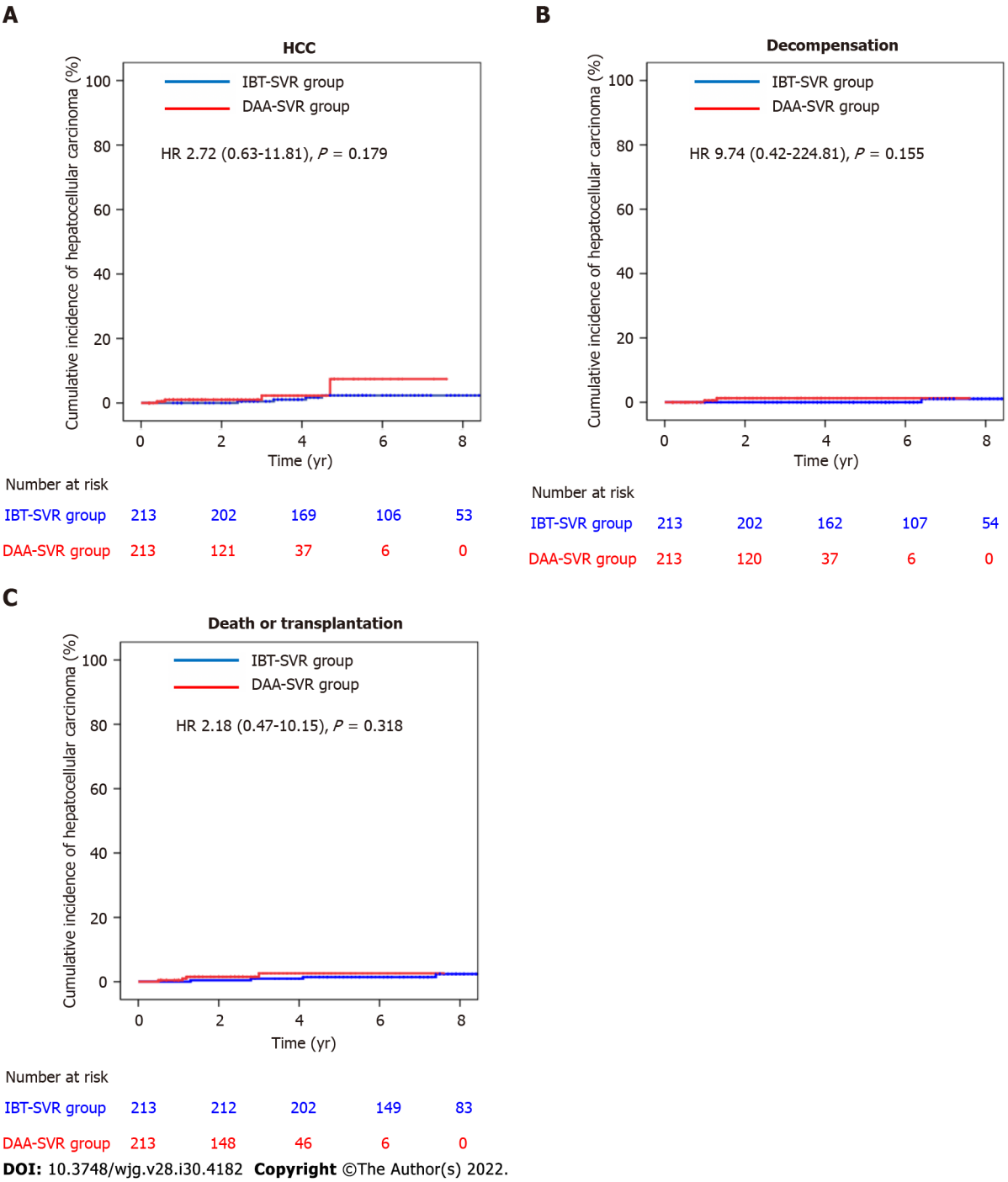
Figure 2 Cumulative incidences of hepatocellular carcinoma, decompensation, and death/transplantation in entire cohort. A: Cumulative incidence of hepatocellular carcinoma in the untreated, interferon-based treatment (IBT), and direct-acting antivirals (DAA) groups; B: Cumulative incidence of decompensation in the untreated, IBT, and DAA groups; C: Cumulative incidence of death/transplantation in the untreated, IBT, and DAA groups. DAA: Direct-acting antivirals; HCC: Hepatocellular carcinoma; IBT: Interferon-based treatment.

with Child-Pugh B/C cirrhosis[26]. In this context, our study showed an approximately 85% reduction in the risk of decompensation after IBT or DAA treatment in Child-Pugh A patients, with decompensated cirrhotic patients being excluded from enrollment.

This study demonstrated that treatment with IBT and DAA resulted in risk reductions of 72% (median follow-up, 94.8 mo) and 81% (median follow-up, 42 mo) for all-cause mortality, respectively, compared with no treatment after multivariate adjustment. Similar to previous studies[27], our results showed that even IBT, with its probable adverse events and lower SVR rates, had long-term beneficial effects on mortality. Regarding the benefit of DAA treatment, Butt *et al*[28] (n = 6790), using the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) data in the United States in



DOI: 10.3748/wjg.v28.i30.4182

Figure 3 Cumulative incidences of hepatocellular carcinoma, decompensation, and death/transplantation in the matched sustained virologic response cohort. A: Cumulative incidence of hepatocellular carcinoma in the interferon-based treatment-sustained virologic response (IBT-SVR) and direct-acting antivirals-sustained virologic response (DAA-SVR) groups; B: Cumulative incidence of decompensation in the IBT-SVR and DAA-SVR groups; C: Cumulative incidence of death/Liver transplantation in the IBT-SVR and DAA-SVR groups. DAA: Direct-acting antivirals; HCC: Hepatocellular carcinoma; IBT: Interferon-based treatment; SVR: Sustained virologic response.

2017, reported that DAA treatment and the achievement of SVR reduced all-cause mortality by 57% and 43%, respectively, within the first 18 mo of treatment. A prospective cohort study performed in France (n = 9895; follow-up, 33.4 mo) reported a 52% reduction in the risk of all-cause mortality in the DAA-treated group compared with the untreated group in 2019[11]. Compared with these studies, our results showed a higher reduction in the risk of all-cause mortality with DAA treatment. This may be related to the low proportion of patients with advanced fibrosis in the DAA group in our cohort. Additionally, the follow-up duration of this study was relatively longer than the durations used for those studies.

During this study, the achievement of SVR by IBT or by DAA resulted in a 59% reduction in the risk of HCC compared with no treatment or no SVR after multivariable adjustment, similar to previous studies[29,30]. Nonetheless, our results also showed that the HCC risk remained after SVR achievement.

Despite the achievement of SVR, the absolute risk of HCC remains high for patients with cirrhosis; therefore, according to international guidelines, they should be enrolled in an HCC surveillance program[2-4]. However, there is little evidence of the benefits of HCC surveillance for non-cirrhotic chronic HCV patients with SVR, because of the low residual HCC risk. During this study, the non-cirrhotic group had an HCC risk of 0.26 per 100 person-years (5-year cumulative incidence of 1.6%). In particular, the low FIB-4 (5-year cumulative incidence of 0.3%) group had a very low risk of HCC during this study. These results are similar to those of the retrospective REAL-C cohort study that targeted Eastern Asians (5-year cumulative incidence: 1.35 for the non-cirrhotic group and 0.13 for the low FIB-4 group)[30]. These results support the European guidelines, which do not recommend HCC surveillance for fibrosis 0 to 2[4]. However, more long-term follow-up data after achieving SVR are needed.

Identifying the risk factors associated with HCC after SVR is important to the development of a reasonable surveillance strategy. An East Asian retrospective study suggested that among the cirrhotic DAA-SVR group, age older than 60 years, ALBI scores of 2 or 3, and pretreatment AFP > 10 ng/mL were associated with HCC risk; however, among the non-cirrhotic group, only AFP > 10 ng/mL was significant[30]. Additionally, there are many factors associated with HCC risk after SVR, such as clinical factors (age, sex, presence of diabetes, HCV genotype 3, history of IBT), laboratory parameters (platelet count, AFP), and fibrosis stage (determined by histology or estimation by Fibroscan®, FIB-4, APRI, or the presence of esophageal varices) before DAA treatment and at follow-up (determined by Fibroscan®, FIB-4, APRI, alanine aminotransferase, AFP, albuminemia, or VITRO score)[31]. In our study, age, cirrhosis, and HCV genotype 1 (compared with genotype 2) were independent risk factors for HCC after SVR. Therefore, it is necessary to test the HCV genotype even in the therapeutic era of pangenotypic regimens to develop a follow-up strategy after SVR according to the regional distribution of HCV genotypes. These factors should be considered when establishing an optimal HCC prediction model.

Previous studies have suggested a similar risk of HCC development with IBT and DAA treatment [32]. Interestingly, a recent meta-analysis suggested that IBT is better than DAA for preventing the occurrence of HCC in chronic hepatitis C patients after achieving SVR[33]. Biologically, IFN family members, especially class I IFN (IFN-α, IFN-β), have important anti-HCC effects[32]. However, some investigators have suggested that the sudden decrease in viral load caused by DAA treatment causes immune distortion, thus deregulating the antitumor response and releasing precancerous foci from immune surveillance[34,35]. Although it can be explained theoretically, there is little clinical evidence regarding the difference in the HCC risk for patients with DAA-SVR and IBT-SVR. Our results showed significant clinical differences between the IBT-SVR and DAA-SVR groups. Both the multivariable analysis and PS matching analysis showed that the effect of IBT-SVR was not different from that of DAA-SVR on the HCC incidence and all-cause mortality. Recently, some studies reported different effects of IBT-SVR and DAA-SVR on the incidence of diabetes[36] and hematologic malignancies[37]. Therefore, long-term studies of the effects of DAA-SVR are warranted.

To meet the 2030 HCV elimination target of the WHO[1], active testing and enhanced linkage to treatment are important. In this study, 30.1% of patients remained untreated, and this percentage should be reduced. Indeed, the untreated group showed a higher mortality rate of 23.7% (88 Liver related deaths and 59 non-liver related deaths) during the median follow-up of 5.6 years. In the untreated group, 3 patients received IBT after HCC diagnosis, and 19 patients received DAA treatment after HCC diagnosis or a decompensation event. The majority of the untreated patients (78.8%, 457/619) were enrolled in the Korean HCV cohort before June 2015, when the first DAA was introduced, and 46.7% (289/619) died or were lost to follow-up before June 2015. Although DAA therapy is covered by the National Health Insurance System, 30% of the drug price is an out-of-pocket expense of the patients, equaling to approximately 3000 United States dollars. Even in the DAA era, the main reasons for non-treatment are the relatively high price of DAA, old age, and extrahepatic or advanced hepatic malignancy.

One of the strengths of our study was that it was a long-term study involving a prospective, Asian cohort that included both IBT and DAA groups. This study used a well-established protocol, guidelines and database, and the data, including death outcomes, were verified under government guidance. To date, few reports have evaluated and compared clinical outcomes (HCC, death, and decompensation) after IBT and DAA treatment, especially in Asia, where HCV is less prevalent than HBV.

This study had several limitations. First, because it was an observational study, the findings may show selection and confounding biases. Despite this limitation, it would be useful for comparing the effectiveness of IBT and DAA because of the relatively low incidence of clinical events. Second, we used clinical and radiological criteria to diagnose cirrhosis; therefore, some patients with advanced fibrosis may have been included in the non-cirrhotic group. However, we attempted to correct this point using a non-invasive liver fibrosis biomarker. Third, there was a disparity in the follow-up periods of the IBT and DAA groups because of the later introduction of DAA (since 2015 in Korea). Additional long-term follow-up studies evaluating the outcomes of patients with SVR are warranted. Forth, the presence of anti-HBc IgG in HCV patients has been implicated in HCC development, and a non-negligible risk of HBV inactivation during DAA treatment (0.91%)[38]. However, approximately 30% of our patients were not tested for anti-HBc IgG, and none of the anti-HBc IgG-positive patients were tested for HBV DNA during DAA treatment. Likewise, the role of fatty liver in the outcomes of HCV patients was not

completely evaluated owing to missing data. Finally, compared with the IBT era, diagnostic imaging modalities and treatment options for HCC have improved in the DAA era. Therefore, these points could have affected the clinical outcomes of the IBT and DAA groups.

CONCLUSION

This study showed that antiviral treatment significantly reduced the incidences of HCC, decompensation, and mortality in an Asian population, regardless of the use of IBT or DAA. After achieving SVR, age, the presence of cirrhosis, and HCV genotype 1 were indicators of worse clinical outcomes. Therefore, an adequate HCC surveillance strategy after SVR that considers age, the presence of cirrhosis, and genotype should be developed. Additional studies evaluating the long-term DAA outcomes of SVR patients are also warranted.

ARTICLE HIGHLIGHTS

Research background

Sustained virologic response (SVR) with either interferon-based therapy (IBT) or direct acting antivirals (DAA)-induced SVR significantly reduces the incidence of hepatocellular carcinoma (HCC) and long-term mortality in patients with hepatitis C virus (HCV) infection.

Research motivation

Prospective studies of the long-term outcomes for patients with HCV infection after treatment with IBT or DAA are limited in many Asian countries.

Research objectives

We aimed to elucidate the incidences of HCC and death/transplantation based on treatment with IBT or DAA. And, we aimed to compare the outcomes of the SVR to IBT and DAA. Finally, we aimed to investigate outcome-determining factors after SVR.

Research methods

The cohort included 2054 viremic patients (mean age, 57 years; 46.5% male; 27.4% with cirrhosis) prospectively enrolled at seven hospitals between 2007 and 2019. They were classified as the untreated group (n = 619), IBT group (n = 578), and DAA group (n = 857).

Research results

Compared to the untreated group, the incidences of HCC and death/transplantation were significantly lower in the IBT group and the DAA group. SVR induced by IBT or DAA did not show significant differences in the risk of HCC and all-cause mortality. After achieving SVR, age, presence of cirrhosis, and genotype 1 HCV infection were indicators of worse clinical outcomes.

Research conclusions

Treatment and SVR with either IBT or DAA significantly reduced the incidences of HCC and mortality in the Asian prospective cohort.

Research perspectives

This study was a long-term study involving a prospective, Asian cohort that included both IBT and DAA groups. This study used a well-established protocol, guidelines and database, and the data, including death outcomes, were verified under government guidance.

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FOOTNOTES

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