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Higher risk of hepatocellular carcinoma in chronic hepatitis B vs chronic hepatitis C after achievement of virologic response

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Summary

It is unclear whether the achievement of virologic response modifies the risk of hepatocellular carcinoma (HCC) differently in chronic hepatitis B (CHB) and chronic hepatitis C (CHC). Our aim was to compare the risk of HCC between patients with CHB and CHC who achieved virological response. We analysed data from patients with CHB treated with entecavir (n=2000) or CHC treated with peg-interferon and ribavirin (n=733) at a tertiary hospital from 2004 to 2011. Virological response was defined as serum HBV DNA<15 IU/mL at 1 year of treatment for CHB or the achievement of sustained virologic response for CHC. Virological response was achieved in 1520 patients with CHB (76.0%) and 475 patients with CHC (64.8%). During the median follow-up period of 6 years, 228 patients with CHB (11.4%) and 59 patients with CHC (8.0%) developed HCC. Among patients with virological response, CHB was independently associated with a significantly higher incidence of HCC (hazard ratio, 2.17; 95% CI, 1.30-3.63; *P*=.003) than CHC. Among patients without virological response, there were no differences in HCC incidence between the two cohorts (*P*=.52). In patients with cirrhosis at baseline, the incidence of HCC did not differ between the two cohorts even after achieving virological response (*P*>.99). In conclusion, patients with CHB treated with entecavir were associated with a higher risk of HCC compared to patients with CHC treated with peg-interferon and ribavirin after achieving virological response. However, the risk of HCC did not differ between the two cohorts if the patients had cirrhosis at baseline, even if virological response was achieved.

KEYWORDS
Entecavir, Hepatitis B Virus, Hepatitis C Virus, Peg-interferon

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most frequent cause of cancer mortality in the world, accounting for more than 600 000 deaths each year.[1] HCC has been the fastest rising cause of cancer-related deaths in developed countries during the past two decades and is expected to increase further in the next decade.[2,3] Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is the most frequent causes of HCC.[2-4] Worldwide, it is estimated that 400 millions and 170 millions people are chronically infected with HBV and HCV, respectively, and approximately 54% and 31% of HCC cases are attributed to HBV and HCV infections.[5,6]

The ultimate goal of treating chronic hepatitis B (CHB) or chronic hepatitis C (CHC) is an improvement in patients' survival by preventing, or at least reducing, the development of cirrhosis, liver failure and HCC. Despite remarkable advances in the antiviral treatments for HBV and HCV during the last two decades, sparse data are available on whether the incidence of HCC is decreasing.[1-3] In fact, a recent systematic review demonstrated that HBV and HCV still are the predominant

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalized ratio; IPTW, inverse probability treatment weighting; IQR, interquartile range; NUC, nucleos(t)ide analogue; PS, propensity score; PEG-IFN, peg-interferon; SD, standard deviation; SVR, sustained virologic response; VR, virologic response.

causes of HCC.[4] A possible explanation would be that some precedent risk factors that are not amenable to antiviral therapy might contribute to the development of HCC. Furthermore, few data are available to determine on whether achieving a virologic response (VR) by treatment of CHB modifies the risk of HCC differently compared with achieving a sustained virologic response (SVR) by treatment of CHC.

The primary aim of this cohort study was to compare the risk of HCC between patients with CHB and CHC who achieved VR and SVR, respectively. In addition, we sought to identify the factors that modify the risk of HCC between patient groups.

2 | MATERIALS AND METHODS

2.1 | Study subjects

The source population consisted of two historical cohorts of patients recruited from Asan Medical Center, a 2700-bed academic tertiary referral hospital in Korea (Figure S1). The CHB cohort consisted of 3090 consecutive patients who were treated with entecavir (0.5 mg/day) between January 2007 and December 2011. The CHC cohort included 850 patients who were treated with the combination of peg-interferon (PEG-IFN) and ribavirin between January 2004 and December 2011. Entecavir and PEG-IFN were first approved in 2007 and 2003, respectively, for the treatment of CHB and CHC in Korea.

Patients were excluded if they met any of the following criteria: age younger than 20 years or older than 80 years; death or receipt of a liver transplant within 6 months of treatment; diagnosis of HCC within 1 year of treatment; co-infection with HBV and HCV, or with any other hepatotrophic viruses; or prior treatment with any other antiviral agent for >2 weeks. In the CHB cohort, patients were also excluded if they had any of the following: serum HBV DNA level <2000 IU/mL at baseline, duration of therapy with entecavir <6 months or loss of hepatitis B surface antigen (HBsAg) within 6 months of treatment. CHC patients with suspected acute HCV infection were also excluded.

Patients with genotype 1 HCV had been treated with PEG-IFN α-2a (Pegasys; Roche, Basel, Switzerland) at a dosage of 180 μg/week or PEG-IFN α-2b (PegIntron; Merck, Kenilworth, NJ, USA) at a dosage of 1.5 μg/kg/week and ribavirin (Robavin; Shinpoong, Seoul, Korea) at a dose of either 1000 mg (for body weights <75 kg) or 1200 mg (for body weights ≥75 kg) for 48 weeks. Patients with genotype 2 or 3 HCV had been treated with PEG-IFN α-2a or PEG-IFN α-2b (at the same doses as for genotype 1) and ribavirin at a dose of 800 mg for 24 weeks.

This study was approved by the Institutional Review Board of Asan Medical Center, and the requirement for informed consent from patients was waived.

2.2 | Outcomes and follow-up

The primary outcome of this study was the development of HCC. The index date was defined as the first date that the patient started antiviral treatments. The patients were followed up from the index date to the diagnosis of HCC or the last follow-up date (31 December 2015). Data about baseline patient characteristics, antiviral treatments, virologic responses and clinical outcomes were obtained from the electronic medical records of Asan Medical Center. To validate the complete set of follow-up data, we obtained information about vital status from the National Population Registry of the Korea National Statistical Office using unique personal identification numbers. Information regarding the primary diagnosis of HCC was validated by accessing the Korean National Health Insurance Service database, which covers more than 99% of the entire Korean population, has a high HCC registration rate (96.5%) and highly accurate diagnostic data, and has been validated as a valid resource for research.[7]

At baseline, patients in both groups underwent an evaluation including medical history taking, physical examination, laboratory testing and abdominal ultrasonography. Cirrhosis was diagnosed based on histological and/or radiological findings with evidence of portal hypertension (eg, splenomegaly, ascites or varices) in the presence of significant thrombocytopenia (platelet count <150 000/mm^3). Serum HBV DNA levels or HCV RNA levels were measured regularly during and after the antiviral therapy. Patients were screened for HCC by ultrasonography and quantification of serum alpha-fetoprotein at baseline and every 6 months during the follow-up period. The diagnosis of HCC was based on the reports of histologic examination and/or typical image patterns (nodule >1 cm with arterial hypervascularity and portal/delayed-phase washout) by dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) as recommended.[5,6]

2.3 | Serum assays

Serum HBV DNA levels were determined using a real-time polymerase chain reaction assay (lower level of detection, 15 IU/mL; Abbott Laboratories, Chicago, IL). The HBV genotype was not determined because more than 98% of Korean patients with CHB have HBV genotype C2.[8] Serological markers, including HBsAg, antibody to hepatitis B surface antigen, hepatitis B e antigen (HBeAg) and antibody to hepatitis B e antigen, were detected using enzyme immunoassays (Abbott Laboratories). Serum HCV RNA levels were quantified (AMPLICOR HCV Test v2.0, Roche, Basel, Switzerland) at pretreatment and at 12, 24 and 48 weeks for all genotypes; they were also quantified at week 72 for patients with genotype 1. The HCV genotype was determined using the restriction fragment mass polymorphism assay.

Routine laboratory parameters, including serum aspartate aminotransferase and alanine aminotransferase (ALT) levels, albumin and total bilirubin concentrations, and international normalized ratio (INR) for prothrombin time, were measured using standard laboratory procedures. The upper limit of normal ALT was defined as 30 IU/L for men and 19 IU/L for women.

2.4 | Statistical analysis

Baseline characteristics of the patients were compared by the chi-square test and Student's *t* test for categorical and continuous variables, respectively. Cumulative incidence curves for the HCC rate were estimated using the Kaplan-Meier method. Two cumulative incidence curves between the CHB and CHC groups were compared with the log-rank test. We also fitted a Cox proportional hazards regression model to obtain the hazards ratio to the HCC incidence. Univariate and multivariable

regression models were used, and the proportionality assumptions were examined by the Schoenfeld residual test. In the multivariable model, backward variable elimination approach was used. Adjusting variables in the multivariable analyses were age, gender, serum levels of ALT, albumin, total bilirubin, INR, platelet count and cirrhosis.

To reduce the impact of potential confounding effects between the CHB and CHC groups, significant differences in the baseline characteristics were adjusted by inverse probability treatment weighting (IPTW) and the propensity score (PS)-based matching analysis. The variables that were used to derive propensity scores were age, gender, serum levels of ALT, albumin, total bilirubin, INR, creatinine, platelet count, diabetes mellitus, hypertension, cirrhosis and Child-Turcotte-Pugh (CTP) score. In the IPTW analysis, we focused on the average effect of the treatment on the treated (ATT) which is the effect for those in the CHB cohort.[9] In the PS matching analysis, we used a nearest neighbourhood matching with calliper size 0.2. We considered the covariate balance achieved as long as the absolute standardized difference between the CHB and CHC cohorts is less than 0.2.

All reported *P*-values are two-sided, and *P*-values <.05 were considered significant. SAS (version 9.1, SAS, Cary, NC) and R (version 3.0, http://cran.r-project.org/) softwares were used for statistical analyses. R packages of CBPS and MatchIt were used for the IPTW and the matching analyses, respectively.[10,11]

3 | RESULTS

3.1 | Characteristics of the study population

The study population consisted of 2733 patients who met the inclusion criteria: 2000 patients who were treated with entecavir for CHB and 733 patients treated with PEG-IFN and ribavirin for CHC (Figure S1). The demographic characteristics of the study patients at baseline are presented in Table 1. Compared to patients with CHC, those with CHB were significantly younger (mean, 47 vs 52 years, *P*<.001), were more likely to be male (64.4% vs 53.5%, *P*<.001), had higher levels of serum ALT (101 vs 66 IU/mL, *P*<.001) and were more likely to

TABLE 1 Baseline characteristics of the study patients

	All patients			Patients with virologic response[a]		
	CHB	CHC		CHB	CHC	
Characteristic	n=2000	n=733	*P* value	n=1520	n=475	*P* value
Age, mean±SD (years)	47±11	52±11	<.001	48±10	51±11	<.001
Male sex, n (%)	1288 (64.4%)	392 (53.5%)	<.001	955 (62.8%)	251 (52.8%)	<.001
HBeAg positivity, n (%)	1168 (58.4%)	NA	NA	791 (52.0%)	NA	NA
HCV genotype, n (%)						
1	NA	319 (43.5%)	NA	NA	163 (34.3%)	NA
2	NA	391 (53.3%)	NA	NA	297 (62.5%)	NA
Others	NA	23 (3.2%)	NA	NA	15 (3.2%)	NA
HBV DNA or HCV RNA, mean±SD, $\log_{10}$ IU/mL	7.14±1.64	5.58±0.95	NA	7.06±1.55	5.58±1.01	NA
ALT, median (IQR), IU/mL	101 (53-190)	66 (36-114)	<.001	101 (54-197)	67 (37-120)	<.001
Albumin, median (IQR), g/dL	3.8 (3.4-4.1)	3.9 (3.7-4.1)	<.001	3.8 (3.4-4.1)	3.9 (3.7-4.1)	<.001
Total bilirubin, median (IQR), mg/dL	1.2 (0.9-1.6)	0.9 (0.7-1.1)	<.001	1.2 (1.0-1.6)	0.8 (0.7-1.1)	<.001
INR, median (IQR)	1.10 (1.00-1.20)	1.02 (0.98-1.08)	<.001	1.10 (1.00-1.20)	1.02 (0.98-1.06)	<.001
Creatinine, median (IQR), mg/dL	0.80 (0.70-1.00)	0.80 (0.70-0.90)	.11	0.80 (0.70-0.90)	0.80 (0.70-0.90)	.54
Platelets, median (IQR), ×1,000/mm^3	142 (96-183)	158 (119-206)	<.001	137 (93-177)	172 (132-211)	<.001
Diabetes mellitus, n (%)	77 (3.9%)	74 (10.1%)	<.001	58 (3.8%)	49 (10.3%)	<.001
Hypertension, n (%)	102 (5.1%)	118 (16.1%)	<.001	80 (5.3%)	78 (16.4%)	<.001
Cirrhosis, n (%)	815 (40.8%)	120 (16.4%)	<.001	670 (44.1%)	46 (9.7%)	<.001
Compensated	530 (65.0%)	99 (82.5%)	<.001	451 (67.3%)	43 (93.5%)	<.001
Decompensated[b]	285 (35.0%)	21 (17.5%)		219 (32.7%)	3 (6.5%)	
CTP score, median (IQR)	5 (5–6)	5 (5-5)	<.001	5 (5–6)	5 (5-5)	<.001
Duration of treatment, median (IQR), months	57.8 (32.4-75.6)	6.3 (5.5-11.5)	NA	60.1 (40.8-78.0)	6.3 (5.8-11.5)	NA
Duration of follow-up, median (IQR), years	5.8 (4.8-7.0)	8.0 (6.1-9.0)	<.001	5.7 (4.8-7.0)	8.0 (6.2-9.0)	<.001

[a]Virologic response was defined as serum HBV DNA <15 IU/mL at 1 year of entecavir therapy and undetectable HCV RNA levels at 24 weeks after cessation of treatment in the CHB and CHC cohorts, respectively.
[b]Decompensated cirrhosis was defined as Child-Pugh score ≥7.
ALT, alanine aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; NA, not applicable; SD, standard deviation.

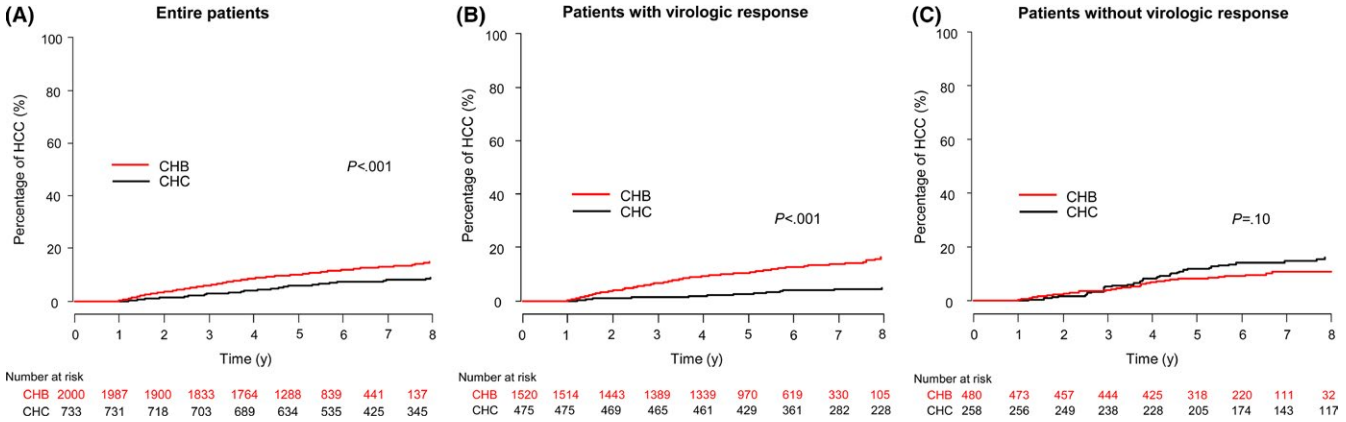

FIGURE 1 Cumulative incidences of hepatocellular carcinoma in the patients with chronic hepatitis B or chronic hepatitis C estimated by Kaplan-Meier method. (A) Entire patients. (B) Patients with virologic response. (C) Patients without virologic response

have cirrhosis (40.8% vs 16.4%, *P*<.001). Among the patients in the CHB cohort, 1168 (58.4%) were HBeAg positive. The mean serum HBV DNA levels were 7.14 $\log_{10}$ IU/mL (standard deviation [SD], 1.64 $\log_{10}$ IU/mL). Among the patients in the CHC group, 319 (43.5%) and 391 (53.3%) had HCV genotypes 1 and 2, respectively. The mean serum HCV RNA level was 5.58 $\log_{10}$ IU/mL (SD, 0.95 $\log_{10}$ IU/mL).

Patients with CHB were advised to continue entecavir regardless of the achievement of VR and/or HBeAg seroconversion. The median duration of continued entecavir treatment for patients with CHB was 57.8 months (interquartile range [IQR], 32.4-75.6 months). The cumulative rate of patients with CHB undergoing treatment modification during entecavir therapy was 1.8%, and most of those patients received a combination of a nucleoside analogue and a nucleotide analogue. For patients with CHC, 536 (73.1%) patients (63.6% and 80.3% for genotypes 1 and 2, respectively) received ≥80% of the planned treatment.

3.2 | Virologic response (VR)

VR was defined as serum HBV DNA <15 IU/mL at 1 year of entecavir therapy or the achievement of undetectable HCV RNA levels at 24 weeks after the cessation of treatment (ie, SVR). In the CHB cohort, 1,520 (76.0%) patients achieved VR, and in the CHC cohort, 475 (64.8%) patients achieved SVR (51.1% and 76.0% for genotypes 1 and 2, respectively).

The patients with VR in the CHB cohort were significantly younger (mean, 48 vs 51 years, *P*<.001), were more likely to be male (62.8% vs 52.8%, *P*<.001), had higher levels of serum ALT (101 vs 67 IU/mL, *P*<.001) and were more likely to have cirrhosis (44.1% vs 9.7%, *P*<.001) than those with VR in the CHC cohort (Table 1).

3.3 | HCC incidence by VR

The median follow-up duration was 5.8 years (IQR, 4.8-7.0 years) for the CHB cohort and 8.0 years (IQR, 6.1-9.0 years) for the CHC cohort (*P*<.001; Table 1). To minimize inequalities in follow-up duration between the two cohorts, we censored patients who were followed for more than 9 years at 9 years of follow-up. During the follow-up period, 228 (11.4%) patients with CHB and 59 (8.0%) patients with CHC developed HCC.

In the entire group of patients, the overall incidence of HCC was significantly higher in the CHB cohort than in the CHC cohort (*P*<.001; Figure 1A). The estimated 5- and 8-year cumulative incidence of HCC was 9.9% and 15.0%, respectively, for the CHB cohort and 5.7% and 8.7%, respectively, for the CHC cohort.

Among the patients with VR, the incidence of HCC was also significantly higher in the CHB cohort than in the CHC cohort (*P*<.001; Figure 1B). The estimated 5- and 8-year cumulative incidence of HCC was 10.5% and 16.3%, respectively, for the CHB cohort and 2.6% and 4.8%, respectively, for the CHC cohort. By multivariable analyses, CHB was independently associated with a significantly higher incidence of HCC (hazard ratio [HR], 2.17; 95% confidence interval [CI], 1.30-3.63; *P*=.003; Table 2).

Among the patients without VR, the incidence of HCC was not significantly different between the CHB and CHC cohorts by Kaplan-Meier estimates (*P*=.10; Figure 1C) and by multivariable analysis (HR, 0.85; 95% CI, 0.52-1.39; *P*=.52; Table S1).

The three competing outcomes in our study were death, transplantation, and HCC. To avoid the potential bias in the interpretation of the cumulative incidence of HCC, we conducted competing risks analysis adjusting for the probability of death and liver transplantation. Consequently, in the entire group of patients, the incidence of HCC was significantly higher in the CHB cohort than in the CHC cohort (HR, 2.08; 95% CI, 1.46-2.96; *P*<.001). Among the patients with VR, the incidence of HCC was also significantly higher in the CHB cohort than in the CHC cohort (HR, 4.54; 95% CI, 2.53-8.16; *P*<.001).

3.4 | Subcohort analyses according to cirrhosis

The patients with VR in each cohort were subdivided according to the presence of cirrhosis at baseline. Among patients without cirrhosis, the incidence of HCC was significantly higher in the CHB cohort than in the CHC cohort (*P*=.001; Figure 2A). By multivariable analyses,

TABLE 2 Predictive factors of hepatocellular carcinoma in patients with virologic response

	Univariate analysis		Multivariable analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
CHB cohort[a]	3.66 (2.30-5.83)	<.001	2.17 (1.30-3.63)	.003
Age	1.05 (1.04-1.07)	<.001	1.05 (1.03-1.07)	<.001
Gender (male)	2.29 (1.65-3.17)	<.001	2.65 (1.90-3.71)	<.001
Albumin (g/dL)	0.39 (0.32-0.48)	<.001	0.63 (0.47-0.86)	.003
Total bilirubin (mg/dL)	1.03 (0.99-1.07)	.19	0.98 (0.91-1.06)	.65
INR	3.94 (2.61-5.96)	<.001	0.46 (0.18-1.18)	.11
Platelets (×1000/mm^3)	0.98 (0.98-0.99)	<.001	0.99 (0.99-1.00)	.01
ALT (>5×ULN)[b]	0.28 (0.19-0.41)	<.001	0.53 (0.35-0.79)	.002
Cirrhosis	8.27 (5.95-11.59)	<.001	3.31 (2.10-5.22)	<.001

[a]The risk of HCC in the CHB cohort was compared with that in the CHC cohort as a reference.
[b]The ULN of ALT was defined as 30 IU/L for men and 19 IU/L for women.
Total number of patients, 1995; number of events, 205.
A Cox proportional hazards model with a backward elimination approach was used for multivariable analysis.
ALT, alanine aminotransferase; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; ULN, upper limit of normal.

CHB was independently associated with a significantly higher incidence of HCC in these subcohorts (HR, 7.99; 95% CI, 3.19-19.98; *P*<.001; Table S2). The incidence rates of HCC were 0.74% per year for the patients with CHB and 0.19% per year for the patients with CHC (Table S3).

By contrast, among cirrhotic patients with VR, the incidence of HCC was not significantly different between the two cohorts by Kaplan-Meier estimates (*P*=.62; Figure 2B) or multivariable analysis (HR, 1.00; 95% CI, 0.57-1.77; *P*>.99; Table S2). The incidence rates of HCC were 4.33% per year for the patients with CHB and 4.70% per year for the patients with CHC (Table S3).

3.5 | Inverse probability weighting analysis

After propensity score weighting, baseline characteristics between CHB and CHC patients were balanced both in VR and non-VR subcohorts (Tables S4 and S5). In the inverse probability weighting analysis among patients with VR, CHB was associated with a significantly higher risk of HCC than CHC (HR, 1.97; 95% CI, 1.20-3.22; *P*=.007; Table 3). However, among patients without VR, the risk of HCC was not significantly different between the CHB and CHC cohorts after inverse probability weighting analysis (HR, 0.77; 95% CI, 0.46-1.26; *P*=.30; Table 3).

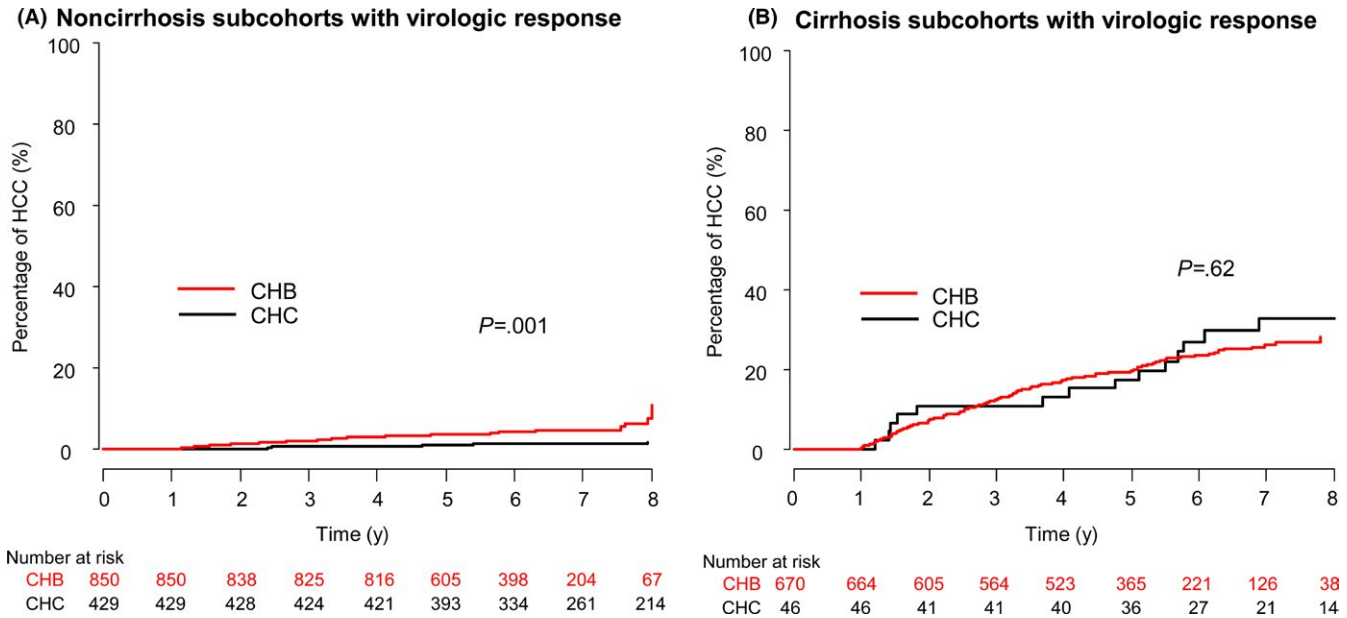

FIGURE 2 Cumulative incidences of hepatocellular carcinoma by cirrhosis at baseline in the patients with virologic response estimated by Kaplan-Meier method. (A) Noncirrhotic patients with virologic response. (B) Cirrhotic patients with virologic response

TABLE 3 Risk of hepatocellular carcinoma of CHB cohort compared with CHC cohort

	Model	HR (95% CI)	*P* value
Virologic response subcohorts	Unadjusted	3.66 (2.30-5.83)	<.001
	Multivariable Cox regression	2.17 (1.30-3.63)	.003
	Inverse probability weighting	1.97 (1.20-3.22)	.007
	PS-matched analysis	2.58 (1.44-4.62)	.001
Nonvirologic response subcohorts	Unadjusted	0.69 (0.45-1.08)	.11
	Multivariable Cox regression	0.85 (0.52-1.39)	.52
	Inverse probability weighting	0.77 (0.46-1.26)	.30
	PS-matched analysis	0.72 (0.37-1.48)	.40

The risk of HCC in the CHB cohort was compared with that in the CHC cohort as a reference.
HR, hazard ratio; CI, confidence interval; PS, propensity score.

3.6 | Propensity score-matched analysis

Propensity score matching analysis was performed for each subcohort of patients with and without VR. After propensity score matching, there were 353 and 170 matched pairs of patients in VR and non-VR subcohorts, respectively. In the propensity score-matched cohort, there were no significant differences between CHB and CHC cohorts (Tables S4 and S5). In the matched patients with VR, CHB was again associated with a significantly higher risk of HCC than CHC (HR, 2.58; 95% CI, 1.44-4.62; *P*=.001; Table 3 and Figure 3). However, in the matched patients without VR, CHB and CHC did not differ in the risk of HCC (HR, 0.72; 95% CI, 0.37-1.48; *P*=.40; Table 3).

3.7 | Inverse probability weighting and propensity score-matched analysis by cirrhosis

The entire cohort was divided into the noncirrhosis and cirrhosis groups according to the presence of cirrhosis at baseline. After propensity score weighting, baseline characteristics between CHB and CHC patients were balanced both in noncirrhosis and cirrhosis groups (Tables S6 and S7). The inverse probability weighting analysis among patients without cirrhosis revealed that CHB was associated with a significantly higher risk of HCC than CHC (HR, 1.93; 95% CI, 1.12-3.32; *P*=.02; Table S8). However, among patients with cirrhosis, the risk of HCC did not significantly differ between the CHB and CHC cohorts (HR, 0.88; 95% CI, 0.58-1.33; *P*=.55).

After propensity score matching, there were no significant differences between CHB and CHC cohorts (Tables S6 and S7). In the matched patients without cirrhosis (440 pairs), CHB was again associated with a significantly higher risk of HCC than CHC (HR, 3.07; 95% CI, 1.47-6.37; *P*=.003; Table S8 and Figure S2). However, in the matched patients with cirrhosis (111 pairs), no meaningful difference in the risk of HCC was found between the CHB and CHC groups (HR, 0.94; 95% CI, 0.56-1.56; *P*=.80).

4 | DISCUSSION

In this observational study, we assessed whether the achievement of VR modifies the risk of HCC differently between patients with CHB and CHC. We found that patients with CHB treated with entecavir had a

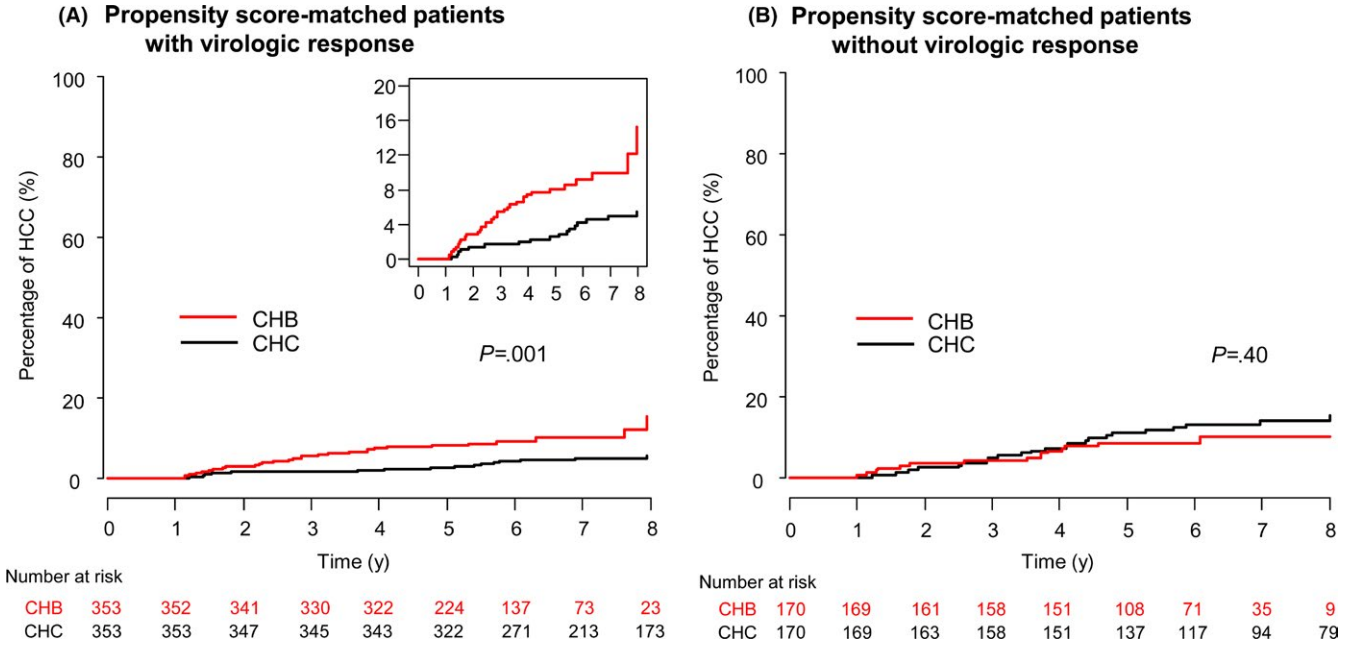

FIGURE 3 Cumulative incidences of hepatocellular carcinoma in the propensity score-matched patients. (A) Patients with virologic response. (B) Patients without virologic response

significantly higher incidence of HCC than patients with CHC treated with PEG-IFN and ribavirin after achieving VR. However, the CHB and CHC cohorts did not differ in incidence of HCC when VR was not achieved or when the patient had cirrhosis at baseline even if VR was achieved. The results were consistently observed by univariate, multivariable, inverse probability weighting and propensity score-matched analyses.

To our knowledge, this is the first study that has directly compared the risk of HCC between patients with CHB and CHC who have achieved VR. VR, which is defined as suppression of the viruses to undetectable serum level by a sensitive polymerase chain reaction assay, has been shown to be associated with reduced risks of mortality and HCC in patients with either CHB or CHC.[12-15] However, the biological significance of VR would differ between CHB and CHC. Achieving SVR after treatment of CHC indicates viral eradication, whereas achieving VR during treatment of CHB suggests suppression of viral replication with HBV remaining in the liver, either integrated into the host genomic DNA or as covalently closed circular DNA.[16] These biological differences of VR between CHB and CHC may explain our findings. The mechanism for the development of HCC is also different between patients with HBV and those with HCV. In patients with CHB, although VR leads to alleviation of hepatic inflammation and can reverse hepatic fibrosis, it may not suffice to prevent HCC development.[17] In contrast, the permanent clearance of HCV by achieving SVR prior to cirrhosis may greatly reduce the risk of HCC.[18] In fact, HBsAg seroclearance after NUC treatment can serve as a sole reliable surrogate marker that is associated with a minimized risk of HCC.[19] It might be worthy to compare the risk of HCC in HCV patients with SVR and HBV patients achieving HBsAg seroclearance. However, not only HBsAg seroclearance after NUC treatment but also the development of HCC after HBsAg seroclearance is so scarce that it might not be appropriate to compare HBsAg seroclearance in CHB with SVR in CHC. Thus, this study compared the risk of HCC between patients who achieved VR in both CHB and CHC.

Our findings are in agreement with the results of previous randomized trials and systematic reviews, which consistently showed that HCC risk can be reduced but not eliminated in CHB patients treated with current potent NUC,[12,14,20,21] while marked reduction in HCC incidence can be observed after treatment that achieves SVR among HCV-infected persons.[12,15] Recent cohort studies have shown that entecavir treatment reduced the risk of HCC and death in CHB patients with cirrhosis compared with no treatment.[22,23] Nonetheless, we found that the risk of HCC persisted to a similar degree in patients with CHB or CHC who had cirrhosis at the time treatment was started. These findings are in line with the fact that cirrhosis is an independent risk factor of HCC for both CHB and CHC, irrespective of VR achievement.[14,24,25] In patients who already have cirrhosis, hepatocytes carrying genetic abnormalities that predispose cancer may be present before the initiation of antiviral treatment. The decision to start HCV treatment early had been hampered by the low efficacy and tolerability of PEG-IFN and ribavirin treatment. This might no longer be the case with the current all-oral direct-acting antiviral agents (DAA) for HCV, which dramatically increase the rate of SVR with minimal adverse effects.

As our patients in different cohorts received different treatments, that is entecavir and PEG-IFN in patients with CHB and CHC, respectively, an intriguing question arises about the effect of treatments on HCC incidence between the two groups. IFN may have an antitumor effect as well as an antiviral effect. Systematic reviews of studies of IFN therapy for patients with CHB have provided conflicting evidence for HBV-related HCC chemoprevention.[12] In contrast, meta-analyses of studies in CHC patients treated with IFN consistently demonstrated a more than 70% reduction in HCC risk occurring independent of the severity of underlying liver fibrosis.[12,15] Because very few patients with CHB are being treated by IFN due to its low efficacy and tolerability and DAAs for CHC only became available as of late 2015 in the country where this study was conducted, this study was not able to compare the two study groups under the same treatment condition. Patients with CHB received IFN-based treatment and patients with CHC received DAA-based treatment are currently attracting attention, the former has the potential beneficial effect of IFN on HCC development, and the latter has the potentially higher risk of HCC development compared with IFN-based treatment.[26] Moreover, the preventive effects of the eradication of HCV on HCC development between IFN-based and DAA-based treatment are still uncertain. Further studies comparing the risks of HCC between patients with CHB and CHC treated by the same regimen are warranted.

The major limitation of this study is that it was based on observational data. Thus, our findings are potentially subject to selection bias and confounding. The unadjusted and adjusted analyses consistently demonstrated a higher risk of HCC in the CHB cohort than in the CHC cohort after VR. However, there may still be some hidden bias due to unmeasured confounders. Despite these limitations, the present observational study is arguably the most reasonable and feasible way to compare the two cohorts because a large sample size and a long-term follow-up period are needed to observe HCC incidence. Secondarily, our study may have limitations for generalization of the results. The predominant population included in this study had genotype C HBV that was acquired through the vertical mode of transmission with a long-duration of infection,[8] and our CHB population had a high prevalence of cirrhosis. These factors might have contributed to the particularly high incidence of HCC in the patients with CHB.[27,28] Third, the data regarding comorbidities such as metabolic syndrome, alcohol abuse and smoking status which might serve as important cofactors for HCC development were not taken into account in the current analysis. Fourth, because we used clinical and radiological criteria for the diagnosis of cirrhosis, some patients with advanced fibrosis or early cirrhosis may be misclassified into noncirrhosis group. Lastly, the number of CHC patients with cirrhosis who achieved VR was relatively small, and the subgroup analysis of them might have insufficient statistical power to demonstrate a significant difference in HCC incidence compared with CHB cohort with cirrhosis.

In conclusion, the present cohort study showed that CHB patients treated with entecavir had a higher risk of HCC than CHC patients treated with PEG-IFN and ribavirin when they achieved VR. However, the risk of HCC was high and did not differ between CHB and CHC patients in the presence of pre-existing cirrhosis. These results suggest that antiviral treatment should be started before the development of cirrhosis in patients with viral hepatitis. Our findings also suggest that HCC surveillance should be continued for CHB patients and cirrhotic CHC patients, regardless of the achievement of VR.

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AUTHOR CONTRIBUTION

GA Kim and YS Lim were responsible for the concept and design of the study, the acquisition, analysis and interpretation of the data, and the drafting of the manuscript. S Han performed the statistical analyses. HD Kim and J An helped with the acquisition of the data and critically revised the manuscript for important intellectual content.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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