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Original Article

Comparison of incidence of hepatocellular carcinoma between chronic hepatitis B patients with cirrhosis treated with entecavir or tenofovir in Taiwan - a retrospective study

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Abstract: Whether tenofovir disoproxil fumarate (TDF) is superior to entecavir in lowering the risk of hepatocellular carcinoma (HCC) development remains controversial. This retrospective study compared the incidences of HCC, cirrhotic events, and mortality between patients treated with entecavir and TDF. The study enrolled 1560 chronic hepatitis B (CHB) patients with cirrhosis from 2008 through 2018. All patients received entecavir or TDF monotherapy for at least 12 months before enrollment. Patients who had HCC or liver transplantation at initial treatment or within the first year of entecavir or TDF therapy were excluded. In the entire cohort, the cumulative incidence rates of HCC at 3, 5, and 10 years were 9.5%, 15.2%, and 25.4%, respectively. The entecavir group had a higher cumulative incidence of HCC than the TDF group (P = 0.001). A Cox regression analysis showed that entecavir group, old age, male sex, hepatic decompensation, diabetes mellitus, lower albumin levels, and platelet count were independent predictors of HCC. TDF treatment was significantly associated with a lower risk of HCC compared to entecavir treatment after adjustment with propensity score matching or inverse probability of treatment weighting in all patients. However, this association was not observed in patients with compensated cirrhosis at entry or patients enrolled after 2011, including after adjustment with propensity score matching or inverse probability of treatment weighting. No significant differences were observed in cirrhotic events and mortality or liver transplantation between the entecavir and TDF groups. In conclusion, the incidences of HCC did not differ significantly between patients with compensated cirrhosis or those enrolled over the same period treated with entecavir or TDF.

Keywords: Entecavir, tenofovir disoproxil fumarate, hepatitis B, cirrhosis, hepatocellular carcinoma

Introduction

Chronic hepatitis B (CHB) is a global health concern and results in cirrhosis, hepatocellular carcinoma (HCC), and death [1]. The goal of antiviral therapy for CHB is to prevent the progression to cirrhosis and its related complications, HCC and death [2-4]. The current treatment guidelines recommend entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) as the first-line nucleos(t)ide analogues (NAs) for the treatment of CHB [2, 3]. These oral agents have potent inhibitory activity against HBV replication, a high genetic barrier to antiviral resistance, and a favorable safety profile. Long-term treatment with entecavir or TDF results in the regression of fibrosis or cirrhosis, as well as reduced rates of cirrhotic complications, HCC, and mortality [5-8].

Two meta-analyses revealed that TDF results in a higher rate of viral suppression at one year of

treatment than entecavir [9, 10]. However, prospective, randomized controlled trials comparing entecavir versus TDF demonstrated that these drugs have similar rates of viral suppression at three years of treatment [11, 12]. Nonetheless, no prospective, head-to-head study has compared the efficacy of entecavir and TDF in reducing the negative outcomes in the long term, such as HCC and mortality.

Two retrospective studies demonstrated a similar risk of HCC in patients treated with entecavir or TDF [13, 14]. Choi et al. first reported that TDF treatment was significantly associated with a lower risk of HCC but not a lower risk of all-cause mortality or transplantation compared with entecavir treatment. That study was conducted with a nationwide cohort study in South Korea, and the result was validated in a hospital cohort [15]. A recent territory-wide retrospective study from Hong Kong also revealed a significantly lower risk of HCC in patients receiving TDF therapy than those receiving entecavir therapy [16]. However, three subsequent studies from South Korea and one study from an international consortium of CHB reported similar effect of TDF and entecavir in reducing the risk of HCC [17-20].

The results among these studies are conflicting. However, there are similar modes of HBV transmission and similar clinical practices for CHB treatment among Asian countries. Therefore, we aimed to investigate the risks of HCC and mortality or transplantation in a multicenter, retrospective cohort of CHB patients with cirrhosis treated with entecavir or TDF in Taiwan.

Materials and methods

Patients

This study retrospectively enrolled a consecutive cohort of 941 CHB patients with cirrhosis who received entecavir treatment between 2008 and 2018, as well as 351 CHB patients with cirrhosis who received TDF treatment between 2011 and 2018. The patients were enrolled from Kaohsiung Chang Gung Memorial Hospital (n = 946) and China Medical University Hospital (n = 346). This study also enrolled another consecutive cohort of 268 CHB patients with cirrhosis who received entecavir (n = 52) or TDF (n = 216) treatment between 2011 and 2018 from Chia-Yi Christian Hospital. In Taiwan, the costs of entecavir and TDF have been reimbursed for HBV treatment by Taiwan's National Health Plan since 2008 and 2011, respectively.

Inclusion criteria

(1) All patients were more than 18 years of age and HBsAg had been positive for more than 6 months prior to NA treatment. (2) All patients had received entecavir or TDF monotherapy for at least 12 months before enrollment. (3) All patients fulfilled the diagnosis of cirrhosis according to either histology (n = 210) or repeated ultrasounds suggestive of cirrhosis and clinical features, such as splenomegaly, gastroesophageal varices, ascites or thrombocytopenia.

Exclusion criteria

(1) Patients had evidence of alcoholic liver disease, autoimmune hepatitis, or coinfection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus. (2) Patients had HCC or liver transplantation at baseline or within the first year of NA treatment.

The study was conducted in accordance with the 1975 Declaration of Helsinki. All patients had signed informed consent before enrollment, and the study was approved by the Research Ethics Committees of Chang Gung Memorial Hospital (202000445B0), China Medical University Hospital (CMUH102-REC1-113), and Chia-Yi Christian Hospital (CYCH-IRB No: 101055).

Methods

During NA therapy, all patients were followed up every 1 to 3 months. Serum alanine aminotransferase (ALT) and HBV DNA levels were measured at baseline, every 3 to 6 months during treatment, and in the event of biochemical breakthrough. All patients were followed until discontinuation of entecavir or TDF therapy or the last visit. HCC surveillance was implemented by abdominal ultrasonography and serum alpha-fetoprotein (AFP) every 3 months. HCC was diagnosed according to the guidelines of the American Association for the Study of Liver Diseases (AASLD) [21].

Definitions

The APRI index was computed by using the aspartate aminotransferase (AST)-to-platelet ratio [22]. The FIB-4 index was calculated by using the following equation: age [years] × AST [U/L]/((platelet [10^9/L]) × (ALT [U/L])$^{1/2}$) [23]. Biochemical response (BR) and virological response (VR) were defined as an ALT level of < 40 U/L and an HBV DNA level of < 20 IU/mL during NA therapy, respectively.

Diabetes mellitus (DM) was diagnosed according to the American Association of Clinical Endocrinologists and American College of Endocrinology guidelines [24]. Patients were also considered diabetic according to their medical history or if they had received insulin treatment or oral hypoglycemic agents. Hypertension was considered diagnosed according a previous diagnosis according to the medical history or having received anti-hypertensive drugs. Cirrhotic events were defined as new developments of ascites, variceal bleeding, or hepatic encephalopathy in patients without hepatic decompensation at the initiation of NA treatment.

Serology

Serum hepatitis B virus (HBV) DNA was quantified using the COBAS AmpliPrep-COBAS TaqMan HBV test with a lower detection limit of 20 IU/mL.

Statistical analysis

Continuous variables are presented as the median ± interquartile range and were compared between groups using the Mann-Whitney U test. Categorical variables were analyzed with the chi-squared test as appropriate. Kaplan-Meier analysis with the log-rank test was used to compare the cumulative incidences of HCC, cirrhotic events, and mortality among groups. Factors associated with HCC, cirrhotic events, or mortality were identified by Cox proportional hazards regression analyses.

Variables with a p value of < 0.25 in the univariate analysis were subjected to stepwise multivariate analysis. Cox proportional hazards regression models with the forward method were used to determine independent factors, and variables with p values < 0.05 were retained in the models. Missing data were assumed to be missing at random and were replaced with substituted values by multiple imputation [25]. All statistical tests were two-sided, and a p value of < 0.05 was considered statistically significant.

We used the propensity score (PS)-matching method to reduce the differences in clinical parameters between the entecavir and TDF groups by creating a ratio of 1:1. The variables included age, sex, DM, hypertension, decompensation, NA experience, baseline AST, ALT, total bilirubin, INR, albumin, platelet, estimated glomerular filtration rate (eGFR), FIB-4, APRI, HBV DNA, HBeAg status, and AFP in the entecavir and TDF groups. Pairs (ETV and TDF groups) on the propensity score logit were matched to within a range of 0.2 SD [26, 27]. For the Inverse Probability of Treatment Weighting (IPTW) method, we used the average treatment effect for treatment weighting by assigning a weight of 1 to the TDF-treated subjects and PS/(1-PS) of the entecavir-treated subjects [28].

Results

Characteristics of all patients in the entecavir and TDF groups at baseline

In the entire cohort (n = 1560), the median treatment duration was 260 weeks (range: 52-732 weeks). The median treatment duration in the entecavir and TDF groups were 312 weeks (range: 52-732 weeks) and 209 weeks (range: 52-422 weeks), respectively. **Table 1** compares the characteristics of all patients treated with entecavir (n = 993) or TDF (n = 567). Patients in the entecavir group had higher percentages of hepatic decompensation, NA naïve status, DM, and hypertension. They also had lower albumin levels, platelet count, and eGFR, as well as higher values of INR, Child-Pugh score, and FIB-4 than those in the TDF group.

Incidence and predictors of HCC for all patients

In the entire cohort, 244 subjects developed HCC during 7704.25 person-years of follow-up. The incidence of HCC was 3.2 (95% confidence interval (CI): 3.1-4.1) per 100 person-years. The cumulative incidences of HCC at 3, 5, and 10

Table 1. Baseline characteristics of patients treated with entecavir or TDF

Variables	Entecavir *n* = 993	TDF *n* = 567	*p* value
Age (year)	55.4 ± 11.7	54.5 ± 12.9	0.190
Sex, male	721 (72.6%)	428 (75.5%)	0.215
HBeAg-positive status	209 (21.0%)	130 (22.9%)	0.377
Decompensation status	182 (18.3%)	58 (10.2%)	< 0.001
NA-naïve	875 (88.1%)	478 (84.3%)	0.033
Diabetes mellitus, yes	232 (23.4%)	89 (15.7%)	< 0.001
Hypertension, yes	280 (28.2%)	131 (23.1%)	0.028
HBV DNA, log_{10} IU/mL	5.42 ± 1.49	5.37 ± 1.44	0.534
AST, U/L	117.4 ± 214.3	113.1 ± 262.9	0.727
ALT, U/L	139.1 ± 268.5	151.7 ± 386.1	0.448
Total bilirubin, mg/dL	2.04 ± 3.84	1.57 ± 2.88	0.011
Albumin, g/dL	3.91 ± 0.65	4.07 ± 0.57	< 0.001
INR	1.20 ± 0.28	1.17 ± 0.24	0.018
eGFR, mL/min/1.73 m^2	85.4 ± 29.9	98.0 ± 52.2	< 0.001
Platelet, $\times 10^3/\mu L$	131.1 ± 55.7	150.4 ± 57.1	< 0.001
AFP, ng/mL	32.0 ± 118.4	31.6 ± 113.8	0.952
Child-Pugh score	5.89 ± 1.60	5.49 ± 1.19	< 0.001
FIB-4	5.13 ± 5.43	3.69 ± 3.84	< 0.001
APRI	3.17 ± 6.42	2.59 ± 6.55	0.090

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

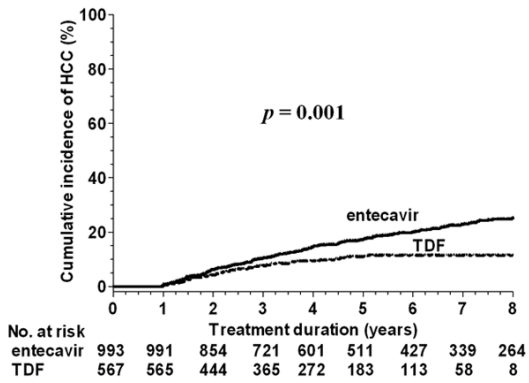

Figure 1. Comparison of HCC incidence between entecavir and TDF for all patients. Abbreviations: HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.

years were 9.5%, 15.2%, and 25.4%, respectively. Of the 993 patients in the entecavir group, 196 developed HCC during 5448.96 person-years of follow-up. The incidence of HCC was 3.60 (95% CI: 3.1-4.2) per 100 person-years. The cumulative incidences at 3, 5, and 8 years were 10.5%, 17.3%, and 25.3%, respectively.

Among the 567 patients in the TDF group, 48 developed HCC during 2255.29 person-years of follow-up. The incidence of HCC was 2.2 (95% CI: 1.6-2.8) per 100 person-years. The cumulative incidences at 3, 5, and 8 years were 7.6%, 10.9%, and 12.8%, respectively. The entecavir group had a higher annual incidence rate of HCC (P < 0.001) and a higher cumulative incidence of HCC than the TDF group (P = 0.001) (**Figure 1**). A Cox regression analysis revealed that entecavir treatment, old age, male sex, hepatic decompensation, DM, lower albumin levels, and platelet count were independent risk factors of HCC for all patients (**Table 2**).

We also analyzed the roles of on-treatment factors, including VR, BR, FIB-4, and AFP at 12 months of treatment in cases of HCC development in 1404 patients who had all data available at month 12. BR, FIB-4, and AFP at 12 months of treatment could predict HCC development. In patients with available data for serum ALT, HBV DNA, FIB-4, and AFP measurements at month 12, TDF-treated patients had a lower risk of HCC than entecavir-treated patients after adjusting for other factors at month 12 (Table S1).

In the 1553 patients with available ALT levels at month 12, the entecavir group had a higher rate of BR than the TDF group (780/990 (78.8%) vs. 397/562 (70.5%), P < 0.001). In the 1432 patients with available HBV DNA levels at month 12, there was no significant difference in VR between the entecavir and TDF groups (820/930 (88.2%) vs. 430/502 (85.7%), P = 0.173). In the entecavir group, the annual incidence rates of HCC were 4.9% and 2.65% within the first 4 years and 5-8 years of therapy, respectively. In the TDF group, the annual incidence rates of HCC were 3.1% and 0.93% within the first 4 years and 5-8 years of therapy, respectively. There was no sig-

Table 2. Univariate and multivariate analyses of factors associated with hepatocellular carcinoma in all patients

Variables	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (year)	1.036 (1.025-1.046)	0.006	1.038 (1.027-1.050)	< 0.001
Sex, male vs. female	1.254 (0.925-1.700)	0.146	1.590 (1.166-2.167)	0.003
HBeAg, yes vs. no	1.045 (0.775-1.408)	0.773		
Decompensation, yes vs. no	2.287 (1.709-3.059)	< 0.001	1.605 (1.094-2.34)	0.015
NA-naïve, yes vs. no	0.928 (0.656-1.312)	0.672		
TDF vs. entecavir	0.585 (0.425-0.806)	0.001	0.672 (0.485-0.930)	0.017
Diabetes mellitus, yes vs. no	1.589 (1.201-2.104)	0.001	1.340 (1.010-1.777)	0.042
Hypertension, yes vs. no	1.634 (1.259-2.122)	< 0.001		
HBV DNA, per $\log_{10}$ IU/mL	1.021 (0.939-1.110)	0.629		
AST, per U/L	1.000 (0.999-1.000)	0.647		
ALT, per U/L	1.000 (0.999-1.000)	0.256		
Total bilirubin, per mg/dL	1.005 (0.971-1.040)	0.786		
Albumin, per g/L	0.553 (0.459-0.666)	< 0.001	0.755 (0.592-0.962)	0.023
INR, per ratio	1.432 (0.969-2.116)	0.071		
eGFR, mL/min/1.73 m^2	0.991 (0.987-0.996)	< 0.001		
Platelet, per 10^3/μL	0.993 (0.991-0.996)	< 0.001	0.996 (0.994-0.999)	0.008
AFP at baseline, per ng/mL	1.000 (0.999-1.001)	0.994		
Child-Pugh score	1.164 (1.087-1.248)	< 0.001		
FIB-4	1.051 (1.035-1.068)	< 0.001		
APRI	1.006 (0.989-1.023)	0.514		

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

nificant difference in the HCC incidence within the first 4 years and 5-8 years in the entecavir group (P = 0.66). However, a significant difference was noted in the HCC incidence within the first 4 years and 5-8 years in the TDF group (P = 0.022).

Subgroup analyses of HCC incidence in the entecavir versus TDF group

Among the 1353 NA-naïve patients, a Cox regression analysis revealed that entecavir treatment, old age, male sex, hepatic decompensation, DM, and lower platelet count were independent predictors of HCC (Table S2). Among the 1320 patients with compensated cirrhosis at baseline, entecavir treatment, old age, male sex, and lower albumin levels and eGFR values were independent predictors of HCC (Table S3). Among the 1153 patients without hepatic decompensation and prior NA experience, a Cox regression analysis identified entecavir treatment, old age, male sex, DM, and lower albumin levels as independent predictors of HCC (Table S4).

TDF has been reimbursed by Taiwan's National Health Plan since 2011. Thus, we conducted a subgroup analysis of the patients treated with entecavir or TDF between 2011 and 2018. Totals of 595 and 567 patients received entecavir and TDF treatment for median durations of 231 and 209 weeks, respectively. A Cox regression analysis showed that old age, male sex, DM, and lower albumin levels were independent predictors of HCC (Table S5). Entecavir treatment was not a significant factor for predicting HCC development in this subgroup.

Comparison of HCC incidences in the entecavir and TDF groups in the entire cohort and different subgroups using PS-matching and IPTW methods

Table S6 shows the baseline characteristics of all patients according to PS matching and IPTW methods. The PS-matching method yielded 545 and 545 patients in the entecavir and TDF groups, respectively. There were no significant differences in clinical characteristics between the two groups according to either meth-

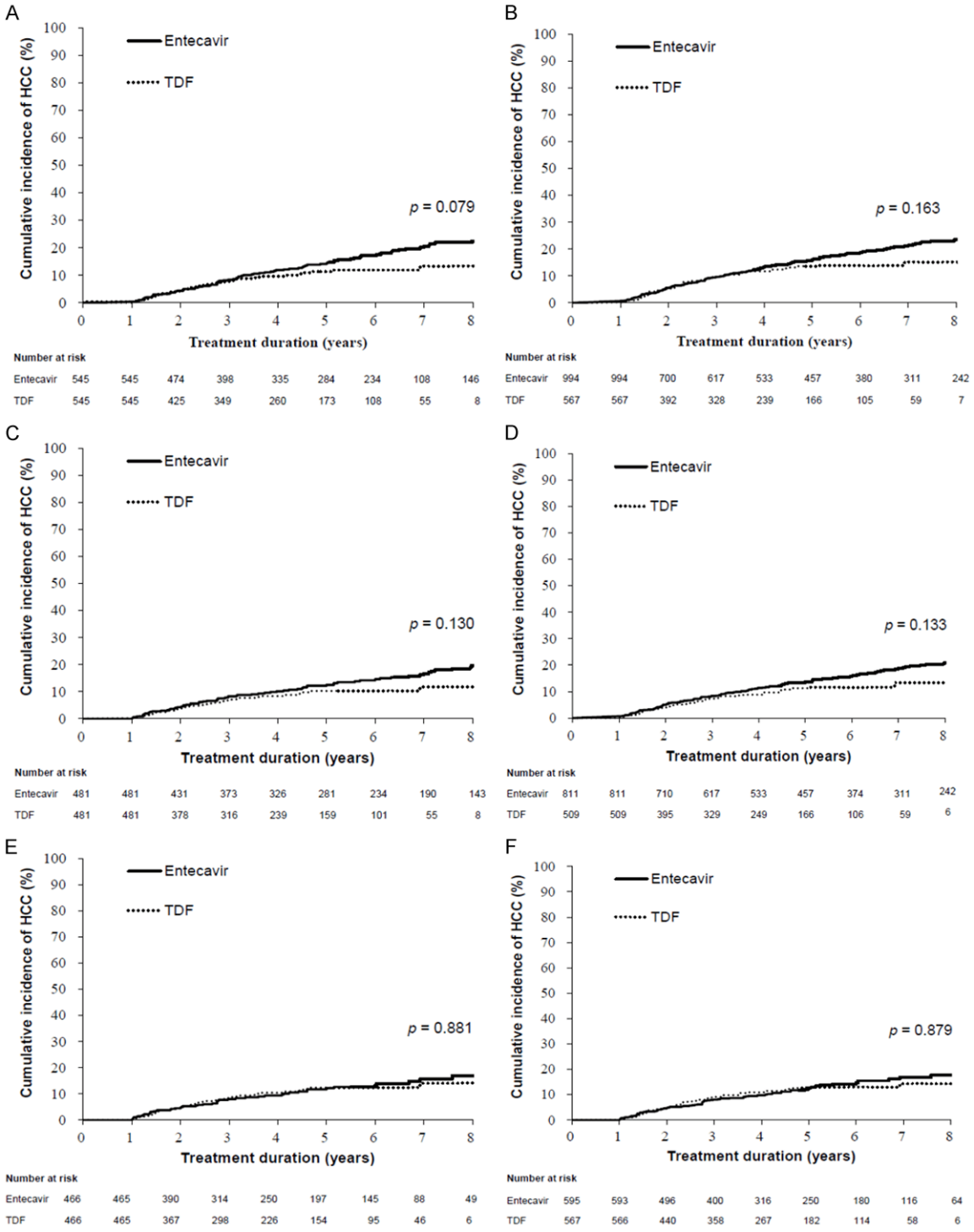

Figure 2. Comparison of HCC incidence between entecavir and TDF according to the PS-matching or IPTW method. All patients (A) and (B), compensated cirrhotic patients (C) and (D), and patients enrolled after 2011 (E) and (F). Abbreviations: IPTW, inverse probability of treatment weighting; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate; PS, propensity score.

od (Table S6). Univariate analysis showed that there was no significant difference in HCC development between entecavir and TDF therapy (**Figure 2A** and **2B**). However, multivariate Cox regression analyses showed that old age, hepatic decompensation, DM, lower platelet

Table 3. Summary of multivariate analyses of factors associated with hepatocellular carcinoma using propensity score matching or inverse probability of treatment weighting in patients who received TDF versus entecavir treatment in all patients and different subgroups

Variables	Propensity Score Matching		Inverse Probability of Treatment Weighting	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
All patients				
Age (year)	1.040 (1.025-1.055)	< 0.001	1.038 (1.027-1.049)	< 0.001
Sex, male vs. female	1.479 (0.965-2.266)	0.073	1.715 (1.250-2.354)	< 0.001
Decompensation, yes vs. no	1.983 (1.223-3.214)	0.006	1.585 (1.082-2.320)	0.018
Diabetes mellitus, yes vs. no	1.630 (1.089-2.438)	0.018	1.416 (1.068-1.877)	0.016
Albumin, per g/L	NS	NS	0.710 (0.556-0.907)	0.006
Platelet, per 10^3/μL	0.996 (0.992-0.999)	0.018	0.997 (0.994-1.000)	0.020
TDF vs. entecavir	0.660 (0.461-0.945)	0.023	0.729 (0.541-0.983)	0.038
Patients with compensated cirrhosis				
Age (year)	1.027 (1.011-1.044)	< 0.001	1.030 (1.017-1.043)	< 0.001
Sex, male vs. female	1.628 (1.013-2.617)	0.044	1.450 (1.010-2.082)	0.044
Diabetes mellitus, yes vs. no	1.573 (1.013-2.442)	0.044	1.362 (0.975-1.903)	0.070
Albumin, per g/L	0.602 (0.410-0.884)	0.009	0.660 (0.494-0.883)	0.005
eGFR, mL/min/1.73 m^2	0.992 (0.985-1.000)	0.040	0.994 (0.989-0.999)	0.028
TDF vs. entecavir		NS	0.720 (0.507-1.022)	0.066
Patients enrolled after 2011				
Age (year)	1.032 (1.014-1.050)	< 0.001	1.030 (1.013-1.048)	< 0.001
Sex, male vs. female	1.698 (1.017-2.836)	0.043	1.736 (1.055-2.856)	0.030
Diabetes mellitus, yes vs. no	1.583 (0.998-2.512)	0.051	1.737 (1.124-2.686)	0.013
Albumin, per g/L	0.588 (0.377-0.918)	0.020	0.600 (0.411-0.877)	0.008
eGFR, mL/min/1.73 m^2	0.992 (0.985-1.000)	0.045	0.991 (0.983-0.998)	0.011
TDF vs. entecavir		NS		NS

CI, confidence interval; eGFR, estimated glomerular filtration rate; NS, no significant difference in univariate analysis; TDF, Tenofovir disoproxil fumarate.

count, and entecavir treatment were independent factors for HCC development after adjustment with PS matching or IPTW (**Table 3**). TDF-treated patients had a lower risk of HCC than entecavir-treated patients (hazard ratios [HRs] of 0.660 and 0.729 according to the PS-matching and IPTW methods, respectively). Male sex and lower albumin levels were significant predictors according to the IPTW analysis.

Table S7 shows the baseline characteristics of patients with compensated cirrhosis at baseline (*n* = 1320) according to the PS-matching and IPTW methods. The PS-matching method yielded 481 and 481 patients in the entecavir and TDF groups, respectively. There were no significant differences in clinical characteristics between the two groups according to either method (Table S7). Multivariate Cox regression analyses revealed that old age, male sex, and lower albumin and eGFR levels were independent factors for HCC development after adjustment with PS matching or IPTW (**Table 3**). DM was a significant predictor according to the PS matching analysis. There were no significant differences in HCC development between patients treated with entecavir and TDF according to the PS-matching or IPTW method (**Figure 2C** and **2D**).

Table S8 shows the baseline characteristics of patients who were enrolled after 2011 (*n* = 1162) according to PS-matching and IPTW methods. The PS-matching method yielded 466 and 466 patients in the entecavir and TDF groups, respectively. There were no significant differences in clinical characteristics between the two groups according to either method (Table S8). Multivariate Cox regression analyses revealed that old age, male sex, and lower albumin and eGFR levels were inde-

Table 4. Univariate and multivariate analyses of factors associated with hepatic evens (new ascites, varices bleeding and hepatic encephalopathy) in patients with compensated cirrhosis at baseline

Variables	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (year)	1.012 (0.992-1.033)	0.236		
Sex, male vs. female	1.193 (0.671-2.122)	0.548		
HBeAg, yes vs. no	0.861 (0.470-1.580)	0.629		
NA-naïve, yes vs. no	1.895 (0.761-4.718)	0.169		
TDF vs. entecavir	0.627 (0.350-1.121)	0.115		
Diabetes mellitus, yes vs. no	1.509 (0.878-2.594)	0.137		
Hypertension, yes vs. no	1.041 (0.611-1.775)	0.881		
HBV DNA, per $\log_{10}$ IU/mL	0.893 (0.757-1.054)	0.180		
AST, per U/L	1.000 (0.998-1.002)	0.706		
ALT, per U/L	0.998 (0.995-1.001)	0.141		
Total bilirubin, per mg/dL	1.057 (0.949-1.176)	0.315		
Albumin, per g/L	0.265 (0.176-0.400)	< 0.001	0.335 (0.217-0.517)	< 0.001
INR, per ratio	1.999 (1.040-3.843)	0.038		
eGFR, mL/min/1.73 m^2	0.995 (0.986-1.003)	0.244		
Platelet, per 10^3/μL	0.983 (0.978-0.989)	< 0.001	0.986 (0.980-0.991)	< 0.001
AFP at baseline, per ng/mL	1.001 (0.997-1.004)	0.674		
Child-Pugh score	1.891 (1.550-2.308)	< 0.001		
FIB-4	1.086 (1.053-1.120)	< 0.001		
APRI	1.023 (0.972-1.076)	0.389		

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

pendent factors for HCC development after adjustment with PS matching or IPTW (**Table 3**). DM was a significant predictor according to the IPTW analysis. There were no significant differences in HCC development between patients treated with entecavir and TDF according to the PS-matching or IPTW method (**Figure 2E** and **2F**).

Incidences and predictors of cirrhotic events

Among the 1320 patients with compensated cirrhosis at baseline, 66 experienced cirrhotic events during treatment, of which 38, 30, and 7 developed ascites, variceal bleeding, and hepatic encephalopathy, respectively. The cumulative incidences of cirrhotic events at 3, 5, and 10 years were 3.2%, 6.3%, and 7.8%, respectively. A multivariate Cox regression analysis revealed that lower albumin levels and platelet count were independent predictors for cirrhotic events (**Table 4**). There were no significant differences in cirrhotic events between patients in the entecavir and TDF groups (P = 0.115).

Incidences and predictors of all-cause and liver-related mortalities

In the entire cohort, 131 subjects developed all-cause mortality during treatment, including 20 patients who underwent liver transplantation. The cumulative incidences of all-cause mortality at 3, 5, and 10 years were 2.4%, 6.3%, and 18.2%, respectively. A multivariate Cox regression analysis revealed that old age, hepatic decompensation, and lower baseline levels of ALT, albumin, and platelet count were independent predictors for all-cause mortality (**Table 5**).

Among the 131 deaths, 98 were liver related. The cumulative incidences of liver-related mortality at 3, 5, and 10 years were 1.9%, 5.3%, and 12.4%, respectively. A Cox regression analysis showed that hepatic decompensation (HR: 2.408, 95% CI: 1.352-4.290, P = 0.003), lower baseline ALT (HR: 0.996, 95% CI: 0.993-0.998, P = 0.002), lower baseline albumin levels (HR: 0.567, 95% CI: 0.386-0.832, P = 0.004), and lower baseline platelet count (HR:

Table 5. Univariate and multivariate analyses of factors associated with all-cause mortality or liver transplantation in all patients

Variables	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (year)	1.033 (1.019-1.048)	< 0.001	1.027 (1.012-1.043)	< 0.001
Sex, male vs. female	1.121 (0.746-1.687)	0.582		
HBeAg, yes vs. no	0.737 (0.469-1.156)	0.184		
Decompensation, yes vs. no	3.538 (2.458-5.093)	< 0.001	2.170 (1.310-3.597)	0.003
NA-naïve, yes vs. no	1.339 (0.782-2.294)	0.288		
TDF vs. entecavir	0.822 (0.527-1.280)	0.385		
Diabetes mellitus, yes vs. no	1.688 (1.163-2.450)	0.006		
Hypertension, yes vs. no	1.171 (0.807-1.700)	0.407		
HBV DNA, per $\log_{10}$ IU/mL	0.937 (0.836-1.050)	0.265		
AST, per U/L	0.999 (0.997-1.000)	0.085		
ALT, per U/L	0.997 (0.996-0.999)	0.008	0.997 (0.995-0.999)	0.001
Total bilirubin, per mg/dL	1.017 (0.977-1.060)	0.408		
Albumin, per g/L	0.400 (0.313-0.511)	< 0.001	0.600 (0.432-0.823)	0.002
INR, per ratio	2.068 (1.332-3.213)	0.001		
eGFR, mL/min/1.73 m^2	0.995 (0.989-1.001)	0.117		
Platelet, per 10^3/μL	0.989 (0.986-0.993)	< 0.001	0.994 (0.990-0.997)	0.001
AFP at baseline, per ng/mL	1.000 (0.999-1.002)	0.559		
Child-Pugh score	1.290 (1.191-1.397)	< 0.001		
FIB-4	1.062 (1.041-1.083)	< 0.001		
APRI	0.998 (0.970-1.026)	0.865		

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

0.991, 95% CI: 0.986-0.995, $P < 0.001$) were independent predictors for liver-related mortality. There were no significant differences in all-cause ($P = 0.384$) or liver-related mortality ($P = 0.107$) between the entecavir and TDF groups.

Discussion

This multicenter, retrospective cohort study examined 1560 predominantly treatment-naïve cirrhotic patients and demonstrated that TDF treatment was associated with a lower risk of HCC than entecavir treatment (HR 0.672, 95% CI: 0.485-0.930). A lower risk of HCC was similarly observed in patients treated with TDF in the PS-matched cohort (HR 0.660, 95% CI: 0.461-0.945) and the IPTW-adjusted cohort (HR 0.729, 95% CI: 0.541-0.983). The multivariate analyses of patient subgroups revealed that TDF treatment was significantly associated with a lower risk of HCC in the treatment-naïve cohort, compensated cirrhotic cohort, and the treatment-naïve compensated cirrhotic cohort, but not in the cohort enrolled after 2011. Moreover, TDF treatment was not associated with a lower risk of HCC in patients with compensated cirrhosis or patients enrolled after 2011 after adjustment with PS matching or IPTW. TDF treatment was not associated with a lower risk of decompensation events in patients with compensated cirrhosis or a lower risk of all-cause or liver-related mortality or transplantation in the entire cohort.

In the present cohort, the risk of HCC was 3.2 (TDF vs. entecavir: 2.2 vs. 3.6) per 100 person-years, and the cumulative incidences of HCC at 3, 5, and 10 years were 9.5%, 15.2%, and 25.4%, respectively (3, 5, and 8 years: TDF vs. entecavir: 7.6%, 10.9%, and 12.8% vs. 10.5%, 17.3%, and 25.3%). A previous multicenter retrospective study examined cirrhotic patients (90% Child A) receiving entecavir therapy for a median duration of 4 years from Taiwan. The study reported an average annual HCC risk of

2.2% with a cumulative incidence of 11.3% at 5 years [7]. Choi et al. reported annual risks of 2.08 vs. 2.76 and 2.12 vs. 3.62 per 100 person-years for TDF vs. entecavir in a PS-matched Korean nationwide cohort and hospital cohort of cirrhotic patients, respectively [15]. Our study cohort comprised 87% treatment-naïve patients and 84.8% compensated cirrhotic patients who received entecavir or TDF therapy for median durations of 312 and 209 weeks, respectively. Therefore, our observation of the annual HCC risk in a similar population of patients was consistent with the two previous studies [7, 15].

Notably, three Korean studies with groups comprising 31.4%, 34.7%, and 40% cirrhotic patients did not find significant differences in HCC incidence between entecavir and TDF in either noncirrhotic or cirrhotic patients [17-19]. These studies excluded patients with decompensated cirrhosis [17, 18] or simultaneously enrolled patients treated with entecavir or TDF during the defined time interval after 2011 (2012 to 2014; 2011 to 2014 for entecavir vs. 2013 to 2015 for TDF) [17, 19]. Yip et al. observed an even greater effect of HCC prevention for TDF in comparison with entecavir (HR 0.39, $P = 0.0016$) in a large-scale population study from Hong Kong, which included only 13.2% cirrhotic patients [16]. However, the small number of cirrhotic patients precluded further comparison of the HCC risk between entecavir and TDF treatment among the cirrhotic subgroup. They speculated that the low percentage of cirrhotic patients might have accounted for the observed lower HR of HCC risk for TDF in their study. This was in consideration of the hypothesis that NA may not reduce the risk of HCC in cirrhotic patients as efficiently as in noncirrhotic patients. However, an alternative interpretation appears to arise from our observation that TDF treatment was associated with a lower risk of HCC in the entire cohort despite after adjustment with PS matching or IPTW, but was not associated with a lower risk of HCC in patients with compensated cirrhosis or patients enrolled after 2011 after adjustment with PS matching or IPTW. We posit that the apparent association of TDF treatment with a lower HCC risk might have resulted from the inclusion of patients with decompensated cirrhosis [15, 16], particularly patients who had received entecavir treatment before 2011, which were the two categories of patients enrolled in previous studies that revealed a lower risk of HCC for TDF [15, 16]. After excluding these patients from analysis, a significant association between TDF treatment and a lower risk of HCC could no longer be demonstrated.

Another interesting observation of this study was that the annual incidence rates of HCC during the first 4 years and during year 5 to 8 were not significantly different in patients treated with entecavir, but they were significantly different in those treated with TDF. It took less time for TDF to exert its full effect of preventing HCC occurrence than entecavir. Hepatocarcinogenesis is a multi-step process that may involve the stepwise disruption of key growth regulatory pathways leading to the development of cancer [29]. A point of no return may exist along the path of cancer development where therapeutic intervention may no longer be able to revert the carcinogenic process. NAs act by inhibiting HBV replication, thereby resolving hepatic necroinflammation, ameliorating angiogenesis, and regressing hepatic fibrosis, thus delaying or preventing the occurrence of HCC [30]. The entecavir cohort preferentially enrolled patients with more advanced cirrhosis, particularly those enrolled before 2011 (Tables S9 and S10). This group may represent patients who are less amenable to HCC prevention by NA therapy.

There are several possible explanations for why TDF treatment was associated with a lower risk of HCC in cirrhotic patients than entecavir treatment. First, the baseline risk of HCC might not be comparable between the two treatment cohorts. Because the cost of entecavir started being reimbursed three years earlier than TDF in Taiwan, patients with more advanced cirrhosis might have been channeled toward entecavir treatment (Group 1 vs. Group 2 and Group 1 vs. Group 3 in Tables S9 and S10). Moreover, patients with co-morbidities such as DM, hypertension, and chronic kidney disease might have been prioritized for entecavir treatment due to safety concerns related to kidney and bone issues, even though both drugs were available for prescription (Group 2 vs. Group 3 in Tables S9 and S10).

Together, these two factors might have imbalanced the severity of liver disease and the confounding risk of HCC among the two treat-

ment cohorts. Indeed, patients in the entecavir group had higher proportions of decompensated cirrhosis, DM, and hypertension, as well as lower albumin levels and platelet count and higher values of INR and FIB-4 than the TDF group. All of these factors are indicative of more advanced liver disease and higher confounding risk of HCC.

To overcome these potential biases, we comprehensively adopted PS matching and IPTW methods to minimize the confounding effects of possible parameters (n = 19) on the observed HCC risk. Despite these statistical approaches, a significantly different effect on the reduction of HCC in favor of TDF treatment was still observed in the entire cohort. However, the association of TDF treatment with a lower HCC risk was no longer observed after we excluded patients with decompensated cirrhosis and, most remarkably, those who started entecavir treatment before 2011. This suggests the possible existence of residual bias due to unmatched or unmeasured confounding in patients enrolled before 2011.

The second possible explanation is that the entecavir group had a significantly higher rate of BR than the TDF group, and both groups had similar rates of VR at 12 months of treatment. This suggested that neither factor could play a role in the differential effect of TDF versus entecavir on HCC prevention. Third, early animal studies indicated that entecavir has carcinogenic potential and induces tumors in rats and mice at doses higher than those used in humans [31]. However, a large-scale prospective, randomized study with NA treatment for up to 10 years did not reveal significantly different incidences of HCC or non-HCC malignant tumors among patients treated with entecavir or the comparator NA [32]. Thus, there is no convincing evidence in support of this possibility.

Fourth, Murata et al. demonstrated that nucleotide analogues (adefovir and TDF) but not nucleoside analogues (lamivudine and entecavir) induced the expression of interferon λ3 in patients with CHB during treatment [33]. Interferon λ3 shows potent antitumor activity in murine models of cancer, including HCC [34]. Perhaps, TDF acts in a similar manner to exert some additional antitumor effect against HCC that we observed in this study. Further study is warranted to test this hypothesis.

Entecavir and TDF showed similar efficacy in preventing cirrhotic events, all-cause mortality, and liver-related mortality. Predictors of cirrhotic events in compensated patients or predictors of mortality in the entire cohort are more reflective of the remaining hepatic reserve (albumin level and hepatic decompensation) and the degree of portal hypertension (platelet count) at the time of treatment initiation. Entecavir and TDF exhibit comparable antiviral potency and therapeutic efficacy during treatment, so it is expected that both drugs would recover liver function and improve these clinical outcomes similarly. In this regard, our findings are consistent with those of previous studies [15, 17-19].

A strength of this study is that we enrolled a large cohort of cirrhotic patients with detailed baseline characteristics, adequate follow-up periods (median: 5 years), and a significant number of incident events. This enabled us to investigate the incidence rates and predictors of HCC, cirrhotic events, and mortality during entecavir or TDF treatment. Most importantly, it also allowed us to compare the effectiveness for preventing such outcomes between entecavir and TDF in different patient subgroups, such as patients with compensated cirrhosis and patients enrolled over the same period.

Nevertheless, there are several limitations to note. First, this was a retrospective analysis of two treatment cohorts enrolled from two tertiary medical centers and one regional hospital, which may have introduced selection bias. Nonetheless, we used PS matching and IPTW methods to meticulously adjust the potential biases of the confounding factors to match these two cohorts. Moreover, we conducted subgroup analyses to unveil the residual confounding effect imposed by the imbalanced severity of liver disease among the two treatment cohorts. A large-scale prospective, randomized comparative trial will be the ideal approach to solve this issue.

A second limitation is that cirrhosis was diagnosed based on histology (n = 210) or ultrasonographic findings plus clinical features of portal hypertension. This was done because liver biopsy was not a routine clinical practice, and noninvasive diagnostic modalities such as FibroScan were not available during a large part of the study period. It is possible that

patients with early cirrhosis might have been underdiagnosed and excluded from enrollment. The proportion of patients with at least a moderate degree of cirrhosis might have been overrepresented, and the overall annual incidence of HCC might have been overestimated in the present cohort (3.2 per 100 person-years). Moreover, this diagnostic uncertainty of the severity of liver cirrhosis might have affected the main aim of this study, which was to compare the effectiveness for preventing clinical outcomes among entecavir and TDF.

Third, despite the inclusion of a list of key baseline clinical characteristics for analysis, we lacked information on body mass index, alcohol use, smoking habit, HBV genotype, and quantitative hepatitis B surface antigen (HBsAg), which are also regarded as potential confounding factors. The inclusion of DM and hypertension as baseline parameters might have led to the partial representation of this population. Genotype and HBsAg are not routine tests in clinical practice in Taiwan. Genotypes B and C are the two major genotypes of HBV that cause CHB in Taiwan. We previously demonstrated that these genotypes accounted for 56% and 44% of infections in patients with cirrhosis, respectively. We also showed that neither genotype nor HBsAg is an independent predictor of HCC, cirrhotic events, or liver-related mortality in this population [35].

In conclusion, we have demonstrated that TDF treatment was associated with a lower risk of HCC than entecavir treatment in this retrospective, predominantly treatment-naïve cohort of cirrhotic patients. However, both treatments exhibited a similar risk of HCC in patients with compensated cirrhosis and patients who were enrolled after 2011 after adjustment with PS matching or IPTW. Moreover, TDF was not associated with a lower risk of cirrhotic events, all-cause or liver-related mortality, or transplantation in the entire cohort.

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Disclosure of conflict of interest

None.

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Table S1. Univariate and multivariate analyses of on-treatment factors at month 12 associated with hepatocellular carcinoma in patients treated with entecavir or TDF

Parameters	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
TDF vs. entecavir	0.585	0.425-0.806	0.001	0.567	0.412-0.837	0.003
ALT normalization at month 12	0.742	0.562-0.978	0.034	0.738	0.551-0.990	0.042
Undetectable HBV DNA at month 12	0.737	0.509-1.068	0.107			
FIB-4 at month 12	1.042	1.031-1.054	< 0.001	1.093	1.074-1.113	< 0.001
AFP at month 12	1.013	1.010-10.16	< 0.001	1.012	1.009-1.115	< 0.001

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HR, hazard ratio; TDF, tenofovir disoproxil fumarate.

Table S2. Univariate and multivariate analyses of factors associated with hepatocellular carcinoma in NA-naive patients (*n* = 1353)

Variables	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value
Age (year)	1.037 (1.025-1.049)	< 0.001	1.041 (1.028-1.053)	< 0.001
Sex, male vs. female	1.192 (0.865-1.644)	0.283	1.553 (1.119-2.156)	0.008
HBeAg, positive vs. negative	1.055 (0.763-1.457)	0.747		
Decompensation, yes vs. no	2.252 (1.631-3.109)	< 0.001	1.626 (1.058-2.499)	0.027
TDF vs. entecavir	0.523 (0.363-0.752)	0.005	0.582 (0.401-0.843)	0.004
Diabetes mellitus, yes vs. no	1.695 (1.254-2.290)	0.006	1.487 (1.099-2.013)	0.010
Hypertension, yes vs. no	1.665 (1.254-2.211)	0.004		
HBV DNA, per $\log_{10}$ IU/mL	1.000 (0.909-1.000)	0.997		
AST, per U/L	1.000 (0.999-1.001)	0.598		
ALT, per U/L	1.000 (0.999-1.000)	0.253		
Total bilirubin, per mg/dL	0.989 (0.943-1.037)	0.639		
Albumin, per g/L	0.550 (0.448-0.675)	< 0.001	0.765 (0.583-1.004)	0.053
INR, per ratio	1.301 (0.829-2.042)	0.253		
eGFR, mL/min/1.73 m^2	0.991 (0.986-0.996)	< 0.001		
Platelet, per 10^3/μL	0.993 (0.991-0.996)	< 0.001	0.997 (0.994-1.000)	0.031
AFP at baseline, per ng/mL	1.000 (0.999-1.001)	0.826		
Child-Pugh score	1.162 (1.078-1.253)	< 0.001		
FIB-4	1.051 (1.033-1.069)	< 0.001		
APRI	1.004 (0.985-1.023)	0.701		

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S3. Univariate and multivariate analyses of factors associated with hepatocellular carcinoma in patients with compensated cirrhosis at baseline (n = 1320)

Variables	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age (year)	1.033 (1.020-1.045)	< 0.001	1.033 (1.020-1.047)	< 0.001
Sex, male vs. female	1.253 (0.882-1.780)	0.208	1.461 (1.017-2.097)	0.040
HBeAg, positive vs. negative	1.207 (0.864-1.686)	0.270		
NA-naïve, yes vs. no	0.982 (0.648-1.488)	0.931		
TDF vs. entecavir	0.628 (0.438-0.900)	0.011	0.689 (0.475-0.999)	0.049
Diabetes mellitus, yes vs. no	1.554 (1.120-2.156)	0.008	1.340 (0.960-1.871)	0.086
Hypertension, yes vs. no	1.751 (1.300-2.358)	< 0.001		
HBV DNA, per $\log_{10}$ IU/mL	1.030 (0.933-1.137)	0.560		
AST, per U/L	1.000 (0.998-1.001)	0.555		
ALT, per U/L	1.000 (0.999-1.000)	0.326		
Total bilirubin, per mg/dL	1.011 (0.913-1.118)	0.838		
Albumin, per g/L	0.573 (0.433-0.758)	< 0.001	0.658 (0.495-0.874)	0.004
INR, per ratio	1.362 (0.773-2.400)	0.286		
eGFR, mL/min/1.73 m^2	0.990 (0.985-0.995)	< 0.001	0.994 (0.989-1.000)	0.039
Platelet, per 10^3/μL	0.995 (0.992-0.998)	0.001		
AFP at baseline, per ng/mL	1.000 (0.997-1.002)	0.720		
Child-Pugh score	1.264 (1.055-1.515)	0.011		
FIB-4	1.059 (1.033-1.086)	< 0.001		
APRI	1.010 (0.976-1.046)	0.566		

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S4. Univariate and multivariate analyses of factors associated with hepatocellular carcinoma in NA-naïve patients with compensated cirrhosis at baseline (n = 1153)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age (year)	1.033 (1.019-1.046)	< 0.001	1.030 (1.016-1.045)	< 0.001
Sex, male vs. female	1.219 (0.843-1.762)	0.293	1.474 (1.008-2.154)	0.045
HBeAg, positive vs. negative	1.160 (0.808-1.666)	0.422		
TDF vs. entecavir	0.534 (0.355-0.805)	0.003	0.576 (0.379-0.877)	0.010
Diabetes mellitus, yes vs. no	1.604 (1.129-2.279)	0.008	1.428 (1.003-2.035)	0.048
Hypertension, yes vs. no	1.879 (1.366-2.583)	< 0.001		
HBV DNA, per $\log_{10}$ IU/mL	1.016 (0.909-1.136)	0.774		
AST, per U/L	1.000 (0.998-1.001)	0.673		
ALT, per U/L	0.999 (0.998-1.001)	0.359		
Total bilirubin, per mg/dL	1.008 (0.904-1.123)	0.887		
Albumin, per g/L	0.584 (0.430-0.794)	<0.001	0.671 (0.493-0.914)	0.011
INR, per ratio	1.199 (0.609-2.364)	0.599		
eGFR, mL/min/1.73 m^2	0.990 (0.984-0.995)	< 0.001	0.995 (0.989-1.001)	0.075
Platelet, per 10^3/μL	0.995 (0.992-0.998)	0.003		
AFP at baseline, per ng/mL	1.000 (0.997-1.002)	0.720		
Child-Pugh score	1.234 (1.013-1.504)	0.037		
FIB-4	1.059 (1.032-1.087)	< 0.001		

APRI	1.013 (0.973-1.054)	0.529

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S5. Univariate and multivariate analyses of factors associated with hepatocellular carcinoma in patients enrolled after 2011 (*n* = 1162)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (year)	1.037 (1.022-1.052)	< 0.001	1.034 (1.019-1.049)	< 0.001
Sex, male vs. female	1.607 (1.029-2.508)	0.037	1.902 (1.212-2.983)	0.005
HBeAg, positive vs. negative	0.907 (0.589-1.397)	0.657		
Decompensation, yes vs. no	0.717 (0.499-1.030)	0.072		
NA-naïve, yes vs. no	1.752 (1.193-2.573)	0.004		
TDF vs. entecavir	1.987 (1.392-2.837)	< 0.001		
Diabetes mellitus, yes vs. no	1.156 (1.026-1.303)	0.018	1.593 (1.082-2.345)	0.018
Hypertension, yes vs. no	1.000 (0.999-1.001)	0.813		
HBV DNA, per $\log_{10}$ IU/mL	1.000 (0.999-1.000)	0.534		
AST, per U/L	1.009 (0.957-1.064)	0.738		
ALT, per U/L	0.521 (0.405-0.671)	< 0.001		
Total bilirubin, per mg/dL	1.558 (0.938-2.588)	0.087		
Albumin, per g/L	0.987 (0.981-0.993)	< 0.001	0.543 (0.421-0.699)	<0.001
INR, per ratio	0.994 (0.990-0.997)	< 0.001		
eGFR, mL/min/1.73 m^2	0.999 (0.998-1.001)	0.589		
Platelet, per $10^3/\mu L$	1.207 (1.095-1.330)	< 0.001		
AFP at baseline, per ng/mL	1.049 (1.023-1.076)	< 0.001		
Child-Pugh score	1.005 (0.981-1.029)	0.707		
FIB-4	1.037 (1.022-1.052)	< 0.001		
APRI	1.607 (1.029-2.508)	0.037		

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S6. Baseline characteristics of all patients adjusted by propensity score matching or inverse probability of treatment weighting

Variables	Propensity score matching			Inverse probability of treatment weighting		
	Entecavir *n* = 545	TDF *n* = 545	*p* value	Entecavir *n* = 994	TDF *n* = 567	*p* value
Age (year)	54.3 ± 11.8	54.5 ± 12.9	0.718	54.9 ± 11.8	55.0 ± 12.9	0.839
Sex, male	414 (78.0%)	411 (75.4%)	0.832	73.8%	74.0%	0.919
HBeAg-positive status	129 (23.6%)	125 (22.9%)	0.774	22.2%	22.9%	0.742
Decompensation status	55 (10.1%)	57 (10.5%)	0.842	16.3%	15.7%	0.766
NA-naïve	468 (85.9%)	462 (84.8%)	0.608	86.5%	86.9%	0.821
Diabetes mellitus, yes	83 (15.2%)	86 (15.8%)	0.802	20.7%	21.6%	0.675
Hypertension, yes	137 (25.1%)	127 (23.3%)	0.480	26.2%	25.6%	0.792
HBV DNA, $\log_{10}$ IU/mL	5.36 ± 1.44	5.37 ± 1.43	0.896	5.43 ± 1.49	5.36 ± 1.44	0.376
AST, U/L	109.2 ± 221.4	112.7 ± 264.1	0.810	123.0 ± 247.6	133.1 ± 287.3	0.479
ALT, U/L	140.6 ± 285.1	149.6 ± 382.8	0.659	153.4 ± 332.8	154.2 ± 349.9	0.964
Total bilirubin, mg/dL	1.68 ± 3.03	1.58 ± 2.90	0.583	1.89 ± 3.45	1.86 ± 3.37	0.831
Albumin, g/dL	4.06 ± 0.58	4.07 ± 0.57	0.773	3.96 ± 0.63	3.94 ± 0.64	0.529
INR	1.17 ± 0.26	1.16 ± 0.23	0.745	1.19 ± 0.27	1.20 ± 0.28	0.323
eGFR, mL/min/1.73 m^2	93.8 ± 26.9	94.9 ± 28.3	0.516	89.6 ± 31.1	88.62 ± 42.0	0.626
Platelet, $\times 10^3$/μL	147.1 ± 53.7	147.9 ± 54.0	0.804	138.7 ± 58.0	137.49 ± 57.0	0.680
AFP, ng/mL	24.8 ± 73.3	30.8 ± 112.	0.297	33.6 ± 145.9	33.8 ± 111.9	0.967
Child-Pugh score	5.54 ± 1.27	5.49 ± 1.19	0.508	5.79 ± 1.50	5.78 ± 1.56	0.896
FIB-4	3.77 ± 3.45	3.70 ± 3.76	0.771	4.62 ± 4.82	4.82 ± 5.57	0.470
APRI	2.43 ± 5.79	2.60 ± 6.62	0.642	2.98 ± 6.16	3.39 ± 7.66	0.279

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S7. Baseline characteristics of patients with compensated cirrhosis adjusted by propensity score matching or inverse probability of treatment weighting

Variables	Propensity score matching			Inverse probability of treatment weighting		
	Entecavir *n* = 481	TDF *n* = 481	*p* value	Entecavir *n* = 811	TDF *n* = 509	*p* value
Age (year)	55.1 ± 11.7	54.8 ± 13.1	0.791	55.3 ± 11.5	55.2 ± 13.2	0.900
Sex, male	350 (72.7%)	354 (73.6%)	0.771	73.0%	73.5%	0.826
HBeAg-positive status	112 (23.3%)	108 (22.4%)	0.759	22.2%	23.4%	0.600
NA-naïve	416 (86.4%)	421 (87.5%)	0.632	87.4%	87.4%	0.966
Diabetes mellitus, yes	75 (15.6%)	76 (15.8%)	0.929	20.2%	21.5%	0.579
Hypertension, yes	116 (24.1%)	115 (23.9%)	0.940	26.7%	26.1%	0.830
HBV DNA, $\log_{10}$ IU/mL	5.41 ± 1.43	5.37 ± 1.42	0.677	5.43 ± 1.45	5.37 ± 1.44	0.459
AST, U/L	81.0 ± 129.1	74.9 ± 129.8	0.469	85.4 ± 140.5	96.8 ± 185.7	0.233
ALT, U/L	104.0 ± 164.5	103.4 ± 244.9	0.962	109.4 ± 173.0	116.0 ± 263.3	0.617
Total bilirubin, mg/dL	1.05 ± 0.63	1.02 ± 0.85	0.648	1.15 ± 1.26	1.15 ± 1.19	0.956
Albumin, g/dL	4.15 ± 0.47	4.16 ± 0.47	0.692	4.12 ± 0.49	4.1 ± 0.53	0.426
INR	1.13 ± 0.26	1.12 ± 0.14	0.364	1.13 ± 0.21	1.14 ± 0.16	0.625
eGFR, mL/min/1.73 m^2	92.4 ± 24.8	94.4 ± 27.3	0.239	88.9 ± 29.1	88.1 ± 41.5	0.689
Platelet, $\times 10^3$/μL	151.3 ± 53.7	152.7 ± 55.0	0.699	144.6 ± 56.8	142.8 ± 56.3	0.574
AFP, ng/mL	21.2 ± 69.7	20.9 ± 68.7	0.953	21.2 ± 62.0	20.8 ± 63.4	0.923
Child-Pugh score	5.21 ± 0.56	5.17 ± 0.49	0.299	5.26 ± 0.66	5.3 ± 0.69	0.383

FIB-4	3.31 ± 2.70	3.15 ± 2.88	0.373	3.77 ± 3.55	4.04 ± 4.62	0.247
APRI	1.74 ± 3.03	1.64 ± 3.22	0.635	1.98 ± 3.52	2.4 ± 5.17	0.102

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S8. Baseline characteristics of patients enrolled after 2011 adjusted by propensity score matching or inverse probability of treatment weighting

Variables	Propensity score matching			Inverse probability of treatment weighting		
	Entecavir *n* = 466	TDF *n* = 466	*p* value	Entecavir *n* = 595	TDF *n* = 567	*p* value
Age (year)	55.1 ± 11.7	54.6 ± 12.9	0.557	55.0 ± 12.0	55.3 ± 12.9	0.608
Sex, male	342 (73.4%)	341 (73.2%)	0.941	72.9%	72.8%	0.969
HBeAg-positive status	102 (21.9%)	104 (22.3%)	0.875	22.8%	22.4%	0.864
Decompensation status	54 (11.6%)	52 (11.2%)	0.837	17.3%	13.4%	0.065
NA-naïve	417 (89.5%)	405 (86.9%)	0.223	86.8%	87.5%	0.719
Diabetes mellitus, yes	86 (18.5%)	81 (17.4%)	0.669	20.0%	20.3%	0.912
Hypertension, yes	121 (26.0%)	115 (24.7%)	0.651	26%	25.9%	0.995
HBV DNA, $\log_{10}$ IU/mL	5.43 ± 1.42	5.41 ± 1.42	0.793	5.51 ± 1.45	5.35 ± 1.43	0.063
AST, U/L	105.6 ± 203.9	106.4 ± 249.7	0.953	132.5 ± 292.9	124.8 ± 276.7	0.641
ALT, U/L	130.0 ± 255.8	133.7 ± 332.2	0.846	168.1 ± 415.2	146.5 ± 340.8	0.331
Total bilirubin, mg/dL	1.66 ± 2.95	1.51 ± 2.63	0.412	1.75 ± 2.94	1.69 ± 3.04	0.719
Albumin, g/dL	4.04 ± 0.62	4.06 ± 0.57	0.592	3.99 ± 0.65	3.99 ± 0.62	0.861
INR	1.18 ± 0.28	1.16 ± 0.23	0.283	1.18 ± 0.25	1.19 ± 0.27	0.634
eGFR, mL/min/1.73 m^2	90.6 ± 27.1	93.1 ± 28.4	0.169	91.1 ± 31.7	90.8 ± 44.1	0.869
Platelet, $\times 10^3/\mu L$	143.6 ± 55.2	146.9 ± 55.1	0.364	144.1 ± 57.6	142.6 ± 57.5	0.666
AFP, ng/mL	30.5 ± 144.1	30.8 ± 113.8	0.980	33.9 ± 155.0	33.9 ± 117.2	0.993
Child-Pugh score	5.61 ± 1.37	5.51 ± 1.21	0.288	5.77 ± 1.48	5.66 ± 1.44	0.219
FIB-4	4.03 ± 4.13	3.79 ± 3.94	0.367	4.31 ± 4.45	4.47 ± 5.22	0.569
APRI	2.53 ± 5.94	2.51 ± 6.52	0.963	2.96 ± 6.32	3.08 ± 7.27	0.761

AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S9. Comparison of baseline characteristics of patient subgroups (*n* = 1560)

Variables	Subgroup 1 *n* = 398	Subgroup 2 *n* = 595	Subgroup 3 *n* = 567	*p* value 1 vs. 2	*p* value 1 vs. 3	*p* value 2 vs. 3
Age (year)	54.57 ± 11.5	55.89 ± 11.77	54.53 ± 12.9	0.081	0.952	0.060
Sex, male	305 (76.6%)	416 (69.9%)	428 (75.5%)	0.020	0.681	0.033
HBeAg-positive status	87 (21.9%)	122 (20.5%)	130 (23%)	0.608	0.685	0.309
Decompensation status	70 (17.6%)	112 (18.8%)	58 (10.2%)	0.622	< 0.001	< 0.001
NA-naïve	339 (85.2%)	536 (90.1%)	478 (84.3%)	0.019	0.711	0.003
Diabetes mellitus, yes	89 (22.4%)	143 (24%)	89 (15.7%)	0.542	0.009	< 0.001
Hypertension, yes	104 (26.1%)	176 (29.6%)	131 (23.1%)	0.236	0.281	0.012
HBV DNA, $\log_{10}$ IU/mL	5.30 ± 1.54	5.50 ± 1.46	5.37 ± 1.44	0.040	0.466	0.133
AST, U/L	128.1 ± 229.8	110.3 ± 203.2	113.1 ± 262.9	0.212	0.350	0.837
ALT, U/L	158.9 ± 305.9	125.9 ± 239.7	151.7 ± 386.1	0.070	0.748	0.173
Total bilirubin, mg/dL	2.29 ± 4.38	1.87 ± 3.43	1.57 ± 2.86	0.107	0.004	0.103
Albumin, g/dL	3.88 ± 0.60	3.92 ± 0.68	4.07 ± 0.57	0.290	< 0.001	< 0.001

INR	1.21 ± 0.28	1.19 ± 0.27	1.17 ± 0.24	0.313	0.013	0.090
eGFR, mL/min/1.73 m^2	85.25 ± 29.51	85.5 ± 30.21	98.04 ± 52.24	0.894	< 0.001	< 0.001
Platelet, $\times 10^3/\mu L$	122.7 ± 53.56	136.7 ± 56.52	150.4 ± 57.07	< 0.001	< 0.001	< 0.001
AFP, ng/mL	29.11 ± 83.72	33.9 ± 136.8	31.61 ± 113.8	0.494	0.694	0.756
Child-Pugh score	5.92 ± 1.61	5.88 ± 1.60	5.49 ± 1.19	0.690	< 0.001	< 0.001
FIB-4	5.57 ± 5.77	4.83 ± 5.17	3.69 ± 3.86	0.040	< 0.001	< 0.001
APRI	3.59 ± 6.87	2.89 ± 6.09	2.59 ± 6.55	0.102	0.023	0.421

Subgroup 1: patients treated with entecavir before 2011; subgroup 2: patients treated with entecavir after 2011; subgroup 3: patients treated with TDF. AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Table S10. Comparison of baseline characteristics of patient subgroups with compensated cirrhosis (*n* = 1320)

Variables	Subgroup 1 *n* = 328	Subgroup 2 *n* = 483	Subgroup 3 *n* = 509	*p* value 1 vs. 2	*p* value 1 vs. 3	*p* value 2 vs. 3
Age (year)	54.78 ± 11.43	56.02 ± 11.56	55.09 ± 13.03	0.133	0.724	0.230
Sex, male	254 (77.4%)	335 (69.4%)	375 (73.7%)	0.011	0.218	0.132
HBeAg-positive status	71 (21.6%)	106 (21.9%)	112 (22%)	0.919	0.891	0.969
NA-naïve	283 (86.3%)	436 (90.3%)	434 (85.3%)	0.079	0.682	0.016
Diabetes mellitus, yes	67 (20.4%)	118 (24.4%)	79 (15.5%)	0.182	0.0680	< 0.001
Hypertension, yes	84 (25.6%)	148 (30.6%)	120 (23.6%)	0.120	0.503	0.012
HBV DNA, $\log_{10}$ IU/mL	5.31 ± 1.50	5.51 ± 1.41	5.35 ± 1.43	0.060	0.693	0.088
AST, U/L	95.83 ± 170.0	85.95 ± 149.9	74.57 ± 127.7	0.3950	0.053	0.200
ALT, U/L	124.9 ± 203.9	100.4 ± 152.9	103.0 ± 241.0	0.065	0.158	0.841
Total bilirubin, mg/dL	1.32 ± 1.71	1.15 ± 1.4	1.01 ± 0.83	0.132	0.003	0.068
Albumin, g/dL	4.05 ± 0.46	4.12 ± 0.52	4.17 ± 0.47	0.054	< 0.001	0.102
INR	1.15 ± 0.22	1.14 ± 0.23	1.12 ± 0.17	0.505	0.078	0.270
eGFR, mL/min/1.73 m^2	83.88 ± 28.5	84.92 ± 27.74	97.23 ± 51.34	0.605	< 0.001	< 0.001
Platelet, $\times 10^3/\mu L$	127.35 ± 54.1	143.38 ± 53.27	155.16 ± 55.98	< 0.001	< 0.001	< 0.001
AFP, ng/mL	20.99 ± 60.48	22.86 ± 63.52	20.81 ± 68.54	0.675	0.968	0.625
Child-Pugh score	5.33 ± 0.69	5.28 ± 0.73	5.17 ± 0.5	0.301	0.003	0.007
FIB-4	4.73 ± 4.91	3.77 ± 3.25	3.11 ± 2.83	0.002	< 0.001	0.001
APRI	2.64 ± 4.74	1.94 ± 3.5	1.61 ± 3.14	0.023	< 0.001	0.117

Subgroup 1: patients treated with entecavir before 2011; subgroup 2: patients treated with entecavir after 2011; subgroup 3: patients treated with TDF. AFP, alpha-fetoprotein; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; INR, international normalized ratio; NA, nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.