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A multicenter study of entecavir *vs.* tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea

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Background & Aims: It is currently unclear which antiviral agent, entecavir (ETV) or tenofovir disoproxil fumarate (TDF), is superior for improving prognosis in patients with chronic hepatitis B (CHB). Here, we assessed the ability of these 2 antivirals to prevent liver-disease progression in treatment-naïve patients with CHB.

Methods: From 2012 to 2014, treatment-naïve patients with CHB who received ETV or TDF as a first-line antiviral agent were recruited from 4 academic teaching hospitals. Patients with decompensated cirrhosis or hepatocellular carcinoma (HCC) at enrollment were excluded. Cumulative probabilities of HCC and death or orthotopic liver transplant (OLT) were assessed.

Results: In total, 2,897 patients (1,484 and 1,413 in the ETV and TDF groups, respectively) were recruited. The annual HCC incidence was not statistically different between the ETV and TDF groups (1.92 *vs.* 1.69 per 100 person-years [PY], respectively; adjusted hazard ratio [HR] 0.975 [$p = 0.852$] by multivariate analysis). Propensity score (PS)-matched and inverse probability of treatment weighting (ITPW) analyses yielded similar patterns of results (HR 1.021 [$p = 0.884$] and 0.998 [$p = 0.988$], respectively). The annual incidence of death or OLT was not statistically different between the ETV and TDF groups (0.52 *vs.* 0.53 per 100 PY, respectively; adjusted HR 1.202 [$p = 0.451$]). PS-matched and ITPW analyses yielded similar patterns of results (HR 1.248 [$p = 0.385$] and 1.239 [$p = 0.360$], respectively). These findings were consistently reproduced in patients with compensated cirrhosis (all $p > 0.05$).

Conclusions: The overall prognosis in terms of HCC and death or OLT was not statistically different between the ETV and TDF groups. Further studies are needed to validate our results.

Lay summary: It is currently unclear which antiviral agent, entecavir or tenofovir disoproxil fumarate, is superior for improving prognosis in patients with chronic hepatitis B virus infection. In this analysis we found that there was no difference in terms of overall prognosis, including risk of hepatocellular carcinoma, death, or the need for a liver transplant, in patients receiving either antiviral.

Introduction

Chronic hepatitis B (CHB) is the most common chronic viral infection worldwide, affecting approximately 350 million people.[1] Because persistently high hepatitis B virus (HBV) replication is associated with an increased risk of compensated cirrhosis and hepatocellular carcinoma (HCC),[2,3] replication-suppressing antiviral therapy is administered to patients with CHB to prevent liver-disease progression.[4] As a matter of fact, oral antiviral agents, particularly entecavir (ETV), reduce the risk of long-term complications such as cirrhosis and HCC, ultimately improving survival compared to controls.[5,6] Nevertheless, because HBV is rarely eradicated from hepatocytes, most patients with CHB require long-term antiviral therapy.[7,8]

Entecavir and tenofovir disoproxil fumarate (TDF) are potent nucleos(t)ide analogues (NUCs) with a high genetic barrier to resistance.[4,9] Because these 2 antivirals have similar short to intermediate-term clinical efficacy (including virologic, biochemical, serologic, and histologic responses), they are recommended by international practice guidelines as first-line antiviral agents for CHB, together with tenofovir alafenamide (TAF).[4,9,10] Furthermore, ETV and TDF have similar efficacy for preventing liver-disease progression,[11–14] consistent with their similar antiviral effects in treatment-naïve patients with CHB.[15–18] Furthermore, effective rescue regimens may offset

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the potential hazard of virologic breakthrough or genotypic resistance in a very small proportion of patients treated with ETV.[19,20]

Choi *et al.*,[21] using the database of the National Health Insurance Service (NHIS) of South Korea, reported that TDF is associated with a significantly lower risk of HCC (hazard ratio [HR] 0.61) and all-cause mortality or orthotopic liver transplant (OLT) (HR 0.77) compared to ETV in multivariate analysis. However, from a hospital-based validation cohort, TDF reduced the risk of HCC with a marginal significance ($p = 0.04$) and did not prevent all-cause mortality or OLT ($p = 0.44$).

Here, in this large-scale, multicenter cohort study conducted in 4 academic teaching hospitals in South Korea, we assessed the efficacy of ETV and TDF, as first-line antivirals in treatment-naïve patients with CHB, in terms of preventing liver-disease progression.

Patients and methods

Patients

Treatment-naïve patients with CHB who started antiviral therapy with ETV 0.5 mg/day or TDF 300 mg/day (ETV and TDF groups, respectively) from January 1, 2012 to December 31, 2014 in 4 academic teaching hospitals (Yonsei University Severance Hospital, Kyungpook National University Hospital, Korea University Anam Hospital, and CHA Bundang Medical Center) were consecutively screened for eligibility. Because the costs of ETV and TDF are reimbursed by the NHIS in South Korea, beginning in January 2007 and December 2012, respectively, the enrollment period was determined as above. The inclusion criteria were as follows: (1) age ≥19 years, (2) well-preserved liver function, and (3) follow-up duration of at least 6 months. The exclusion criteria were as follows: (1) history of HCC at enrollment, (2) decompensated cirrhosis at enrollment, (3) coinfection with other hepatitis virus, (4) history of organ transplant, (5) development of clinical events (HCC, death, or OLT) within 6 months of enrollment, and (6) other significant medical illness. Owing to the homogenous nature of our study population, data on race/ethnicity were not collected.

In South Korea, the reimbursement criteria for ETV or TDF are identical (Table S1). If histologic information was not available, compensated cirrhosis was clinically defined as follows: (1) platelet count <150,000/μl and ultrasonographic findings suggestive of compensated cirrhosis, including a blunted, nodular liver surface accompanied by splenomegaly (>12 cm); or (2) esophageal or gastric varices.

The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of each participating institution.

Clinical evaluation, follow-up, and outcomes

The diagnosis of hypertension was made when systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥90 mmHg, or if the patient was taking an anti-hypertensive agent. During follow-up, all patients underwent routine blood-chemistry testing and assay of serum HBV-DNA level and other viral markers every 3–6 months. Patients also underwent ultrasonography and assay of serum alpha-fetoprotein level to screen for HCC and cirrhotic complications every 6 months.

The primary outcome was HCC development. HCC was diagnosed based on histological evidence or dynamic computed tomography and/or magnetic resonance imaging findings (nodule >1 cm with arterial hyper-vascularity and portal/delayed-phase washout).[22,23] The secondary outcomes were all-cause mortality and OLT. The index date was the date of the first prescription of ETV or TDF and the follow-up period was between the index date and the date of HCC diagnosis, death, OLT, or the final follow-up.

Statistical analysis

Data are expressed as means ± standard deviation or numbers (%). Differences among continuous and categorical variables were examined for significance by Student's *t* test (or the Mann-Whitney *U* test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate). The cumulative risk of HCC and death or OLT was calculated by the Kaplan-Meier method and was compared using the log-rank test. The multivariate analysis was performed using the Cox proportional hazards model.

To reduce selection bias and the effect of potential confounders, propensity scores (PSs) were calculated by logistic regression based on age, gender, diabetes, hypertension, compensated cirrhosis, and hepatitis B e antigen (HBeAg) status, total bilirubin, albumin, and platelet counts. Differences between the 2 groups were balanced by a 1:1 PS-matched analysis and inverse probability of treatment weighting (IPTW) analysis

Statistical analyses were conducted using SAS (ver. 9.4; SAS Institute) and R software (V.3.4.4, http://cran.r-project.org/). Two-sided *p* values <0.05 were considered indicative of statistical significance.

Results

Baseline characteristics

A total of 2,897 treatment-naïve patients with CHB, treated with ETV (n = 1,484) or TDF (n = 1,413) as the first-line antiviral agent were analyzed (Fig. S1). The baseline characteristics are listed in Table 1. The mean age of the ETV and TDF groups was 48.2 and 48.8 years, respectively ($p = 0.138$). In total, 499 patients (33.6%) in the ETV group had compensated cirrhosis at baseline, compared to 411 (29.1%) in the TDF group ($p = 0.009$). The frequency of HBeAg positivity was not statistically different between the 2 groups (51.1% *vs.* 49.1%; $p = 0.291$). The TDF group had a higher mean platelet count (173.1 *vs.* 165.6 $\times 10^3$/μl; $p = 0.004$) and proportion of males (64.6% *vs.* 59.9%; $p = 0.009$) and a lower mean HBV-DNA level (5.4 *vs.* 5.7 $\log_{10}$ IU/ml; $p < 0.001$). The mean body mass index of the ETV and TDF groups was 23.8 and 23.6 kg/m^2, respectively ($p = 0.198$).

Clinical outcomes among the entire cohort

Among the entire cohort, 240 (8.3%) patients developed HCC during the follow-up, 138 in the ETV group and 102 in the TDF group. The cumulative risk of HCC development at 1, 3, and 5 years was 1.0%, 4.8%, and 9.3% (annual incidence 1.92 per 100 person-years [PY]), respectively, in the ETV group; while it was 1.0%, 4.7%, and 7.7% (annual incidence 1.69 per 100 PY), respectively, in the TDF group ($p = 0.516$) (Fig. 1A), with an HR (reference: ETV group) of 0.917 (95% CI 0.705–1.191; $p = 0.517$). By multivariate analysis, the risk of HCC was not statistically different between the 2 groups (adjusted HR 0.975; 95% CI 0.747–1.272; $p = 0.852$).

Among the entire cohort, 72 (2.5%) patients died or underwent OLT, 39 in the ETV group and 33 in the TDF group. The cumulative risk of death or OLT at 1, 3, and 5 years was 0.5%, 1.8%, and 2.6% (annual incidence 0.52 per 100 PY), respectively,

Table 1. Comparison of baseline characteristics between 2 groups among the entire population.

Variables	ETV group (n = 1,484)	TDF group (n = 1,413)	*p* value*
Age, years	48.2 ± 11.5	48.8 ± 12.0	0.138
Male gender	889 (59.9%)	913 (64.6%)	0.009
Presence of diabetes	121 (8.2%)	106 (7.5%)	0.514
Presence of hypertension	156 (10.5%)	123 (8.7%)	0.099
Body mass index, kg/m^2	23.8 ± 4.5	23.6 ± 2.9	0.198
Compensated cirrhosis	499 (33.6%)	411 (29.1%)	0.009
Positive HBeAg	758 (51.1%)	694 (49.1%)	0.291
Log_{10} HBV-DNA, IU/ml	5.7 ± 2.1	5.4 ± 2.1	<0.001
Prothrombin time, INR	1.0 ± 0.4	0.9 ± 0.4	<0.001
Platelet counts, $\times 10^3/\mu l$	165.6 ± 69.9	173.1 ± 72.2	0.004
Bilirubin, mg/dl	0.78 ± 0.44	0.78 ± 0.42	0.640
Albumin, g/dl	4.14 ± 1.75	4.21 ± 0.46	0.166
Child-Pugh score	5.18 ± 0.44	5.13 ± 0.36	0.001
MELD score	8.01 ± 3.20	7.63 ± 2.49	0.001

Values are expressed as mean ± standard deviation or numbers (%).
*Calculated by Student's *t* test (or the Mann-Whitney *U* test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate)
ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio; MELD, model for end-stage liver disease; TDF, tenofovir disoproxil fumarate.

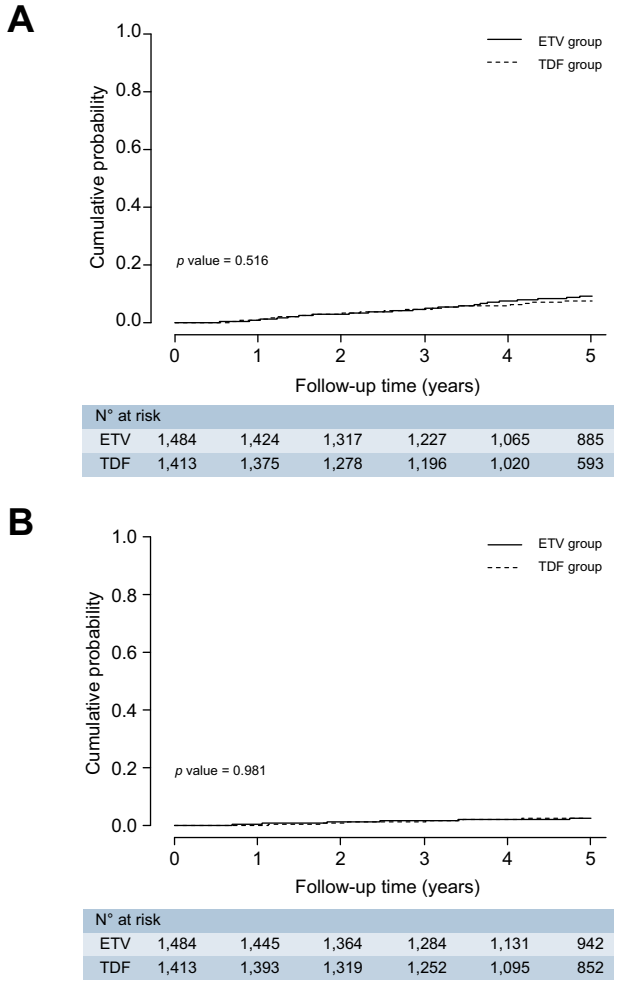

Fig. 1. Cumulative risk of HCC and death or OLT between ETV and TDF groups. Kaplan-Meier curves of (A) HCC and (B) death or OLT in the entire population. ETV, entecavir; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplant; TDF, tenofovir disoproxil fumarate.

in the ETV group; while it was 0.2%, 1.4%, and 2.5% (annual incidence 0.53 per 100 PY), respectively, in the TDF group ($p = 0.981$), with an HR of 1.006 (95% CI, 0.628–1.611; $p = 0.981$) (Fig. 1B). By multivariate analysis, the risk of death or OLT was not statistically different between the 2 groups (adjusted HR 1.202; 95% CI 0.745–1.939; $p = 0.451$).

PS-matched analysis of clinical outcomes among the entire cohort

The 1:1 PS-matched analysis generated 1,278 pairs, and the baseline characteristics of the ETV and TDF groups were described (Table 2). The cumulative risk of HCC development at 1, 3, and 5 years was 1.0%, 4.2%, and 8.7%, respectively, in the ETV group; while it was 1.0%, 4.8%, and 7.9%, respectively, in the TDF group (Fig. 2A; $p = 0.808$), with an HR of 1.021 (95% CI 0.773–1.349; $p = 0.884$). The cumulative risk of death or OLT at 1, 3, and 5 years was 0.5%, 1.5%, and 2.2%, respectively, in the ETV group; while it was 0.2%, 1.4%, and 2.6%, respectively, in the TDF group (Fig. 2B; $p = 0.777$), with an HR of 1.248 (95% CI 0.757–2.056; $p = 0.385$).

IPTW analysis of clinical outcomes among the entire cohort

The baseline characteristics of the ETV and TDF groups were described (Table 2). The cumulative risk of HCC development at 1, 3, and 5 years was 0.9%, 4.5%, and 9.0%, respectively, in the ETV group; while it was 1.0%, 5.0%, and 8.1%, respectively, in the TDF group (Fig. 2C; $p = 0.996$), with an HR of 0.998 (95% CI 0.771–1.293; $p = 0.988$). The cumulative risk of death or OLT at 1, 3, and 5 years was 0.5%, 1.7%, and 2.4%, respectively, in the ETV group; while it was 0.2%, 1.6%, and 2.8%, respectively, in the TDF group (Fig. 2D; $p = 0.303$), with an HR of 1.239 (95% CI 0.783–1.962; $p = 0.360$).

Clinical outcomes among patients with compensated cirrhosis

Among the patients with compensated cirrhosis (n = 910), the baseline characteristics of the ETV and TDF groups were described (Table 3) and 174 (19.1%) developed HCC: 108 in the ETV group and 66 in the TDF group. The cumulative risk of HCC development at 1, 3, and 5 years was 2.4%, 12.1%, and 21.6%, respectively, in the ETV group; while it was 2.2%, 11.0%, and 16.8%, respectively, in the TDF group (Fig. 3A; $p = 0.298$), with an HR of 0.848 (95% CI 0.621–1.158; $p = 0.299$). By multivariate analysis, the risk of HCC was not statistically different between the 2 groups (adjusted HR 0.831; 95% CI 0.606–1.139; $p = 0.250$).

Table 2. Comparison of baseline characteristics between 2 groups after PS-matching and IPTW analysis among the entire population.

	1:1 PS-matching analysis			IPTW analysis		
Variables	**ETV group**	**TDF group**	***p* value***	**ETV group**	**TDF group**	***p* value**
Age, years	48.6 ± 11.4	48.2 ± 12.0	0.381	48.4 ± 0.3	48.3 ± 0.3	0.946
Male gender	793 (62.1%)	794 (62.1%)	0.966	941 (62.2%)	900 (62.1%)	0.964
Presence of diabetes	99 (7.8%)	97 (7.6%)	0.882	120 (7.9%)	116 (8.0%)	0.946
Presence of hypertension	131 (10.3%)	120 (9.4%)	0.451	147 (9.7%)	141 (9.7%)	0.997
Body mass index, kg/m^2	23.72 ± 2.98	23.64 ± 2.90	0.560	23.80 ± 0.12	23.62 ± 0.08	0.224
Compensated cirrhosis	394 (30.8%)	400 (31.3%)	0.787	476 (31.5%)	456 (31.5%)	0.976
Positive HBeAg	640 (50.1%)	640 (50.1%)	>0.999	758 (50.1%)	727 (50.2%)	0.978
Log_{10} HBV-DNA, IU/ml	5.62 ± 2.11	5.55 ± 2.09	0.433	5.63 ± 0.06	5.48 ± 0.06	0.062
Prothrombin time, INR	0.94 ± 0.36	0.89 ± 0.42	0.001	0.95 ± 0.01	0.90 ± 0.01	0.001
Platelet counts, $\times 10^3/\mu l$	169.3 ± 69.7	170.1 ± 71.5	0.760	169.1 ± 1.9	169.0 ± 1.9	0.986
Bilirubin, mg/dl	0.77 ± 0.42	0.77 ± 0.42	0.732	0.78 ± 0.11	0.78 ± 0.01	0.982
Albumin, g/dl	4.16 ± 0.46	4.17 ± 0.45	0.299	4.15 ± 0.01	4.15 ± 0.01	0.895
Child-Pugh score	5.15 ± 0.39	5.14 ± 0.38	0.362	5.15 ± 0.01	5.16 ± 0.01	0.566
MELD score	7.93 ± 3.13	7.69 ± 2.64	0.042	7.92 ± 0.08	7.71 ± 0.07	0.056

Values are expressed as mean ± standard deviation or numbers (%).
*Calculated by paired *t* test or McNemar's test
ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio; IPTW, inverse probability of treatment weighting; MELD, model for end-stage liver disease; PS, propensity score; TDF, tenofovir disoproxil fumarate.

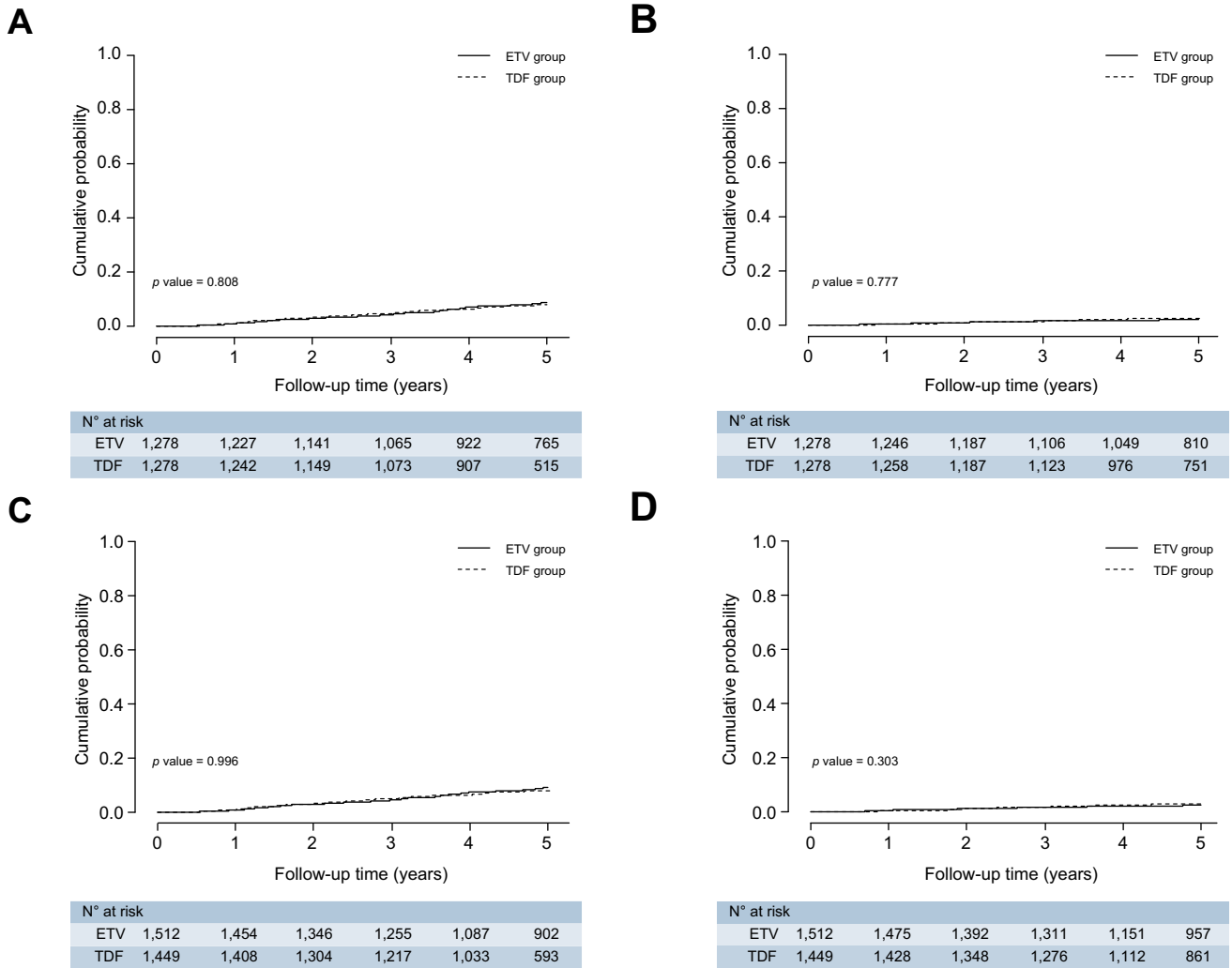

Fig. 2. Cumulative risk of HCC and death or OLT between ETV and TDF groups by PS-matching and IPTW analysis. Kaplan-Meier curves of (A) HCC and (B) death or OLT by PS-matching analysis and of (C) HCC and (D) death or OLT by IPTW analysis among the entire population. ETV, entecavir; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting; OLT, orthotopic liver transplant; PS, propensity score; TDF, tenofovir disoproxil fumarate.

Among the patients with compensated cirrhosis, 42 died or underwent OLT, 21 in the ETV group and 21 in the TDF group. The cumulative risk of death or OLT at 1, 3, and 5 years was 0.6%, 2.5%, and 4.1%, respectively, in the ETV group; while it was 0.2%, 2.3%, and 5.3%, respectively, in the TDF group (Fig. 3B; $p = 0.226$), with an HR of 1.463 (95% CI 0.787–2.722; $p = 0.229$). By multivariate analysis, the risk of death or OLT was not statistically different between the 2 groups (adjusted HR 1.199; 95% CI 0.743–1.935; $p = 0.456$).

PS-matched analysis of the clinical outcomes among patients with compensated cirrhosis

Among the patients with compensated cirrhosis, the 1:1 PS-matched analysis generated 380 pairs, and the baseline characteristics of the ETV and TDF groups were described (Table 4). The cumulative risk of HCC development at 1, 3, and 5 years was 1.9%, 11.4%, and 20.9%, respectively, in the ETV group; while it was 1.9%, 10.0%, and 16.0%, respectively, in the TDF group (Fig. 4A; $p = 0.307$), with an HR of 0.854 (95% CI 0.612–1.193; $p = 0.356$). The cumulative risk of death or OLT at 1, 3, and 5 years was 0.3%, 2.0%, and 3.4%, respectively, in the ETV group; while it was 0.3%, 2.5%, and 5.4%, respectively, in the TDF group (Fig. 4B; $p = 0.221$), with an HR of 1.917 (95% CI 0.924–3.974; $p = 0.080$).

IPTW analysis of the clinical outcomes among patients with compensated cirrhosis

Among the patients with compensated cirrhosis, the baseline characteristics of the ETV and TDF groups were described (Table 4). The cumulative risk of HCC development at 1, 3, and 5 years was 2.4%, 12.2%, and 21.9%, respectively, in the ETV group; while it was 2.1%, 10.8%, and 16.6%, respectively, in the TDF group (Fig. 4C; $p = 0.231$), with an HR of 0.824 (95% CI 0.605–1.123; $p = 0.220$). The cumulative risk of death or OLT at 1, 3, and 5 years was 0.5%, 2.4%, and 4.0%, respectively, in the ETV group; while it was 0.3%, 2.5%, and 5.4%, respectively, in the TDF group (Fig. 4D; $p = 0.140$), with an HR of 1.599 (95% CI 0.864–2.959; $p = 0.135$).

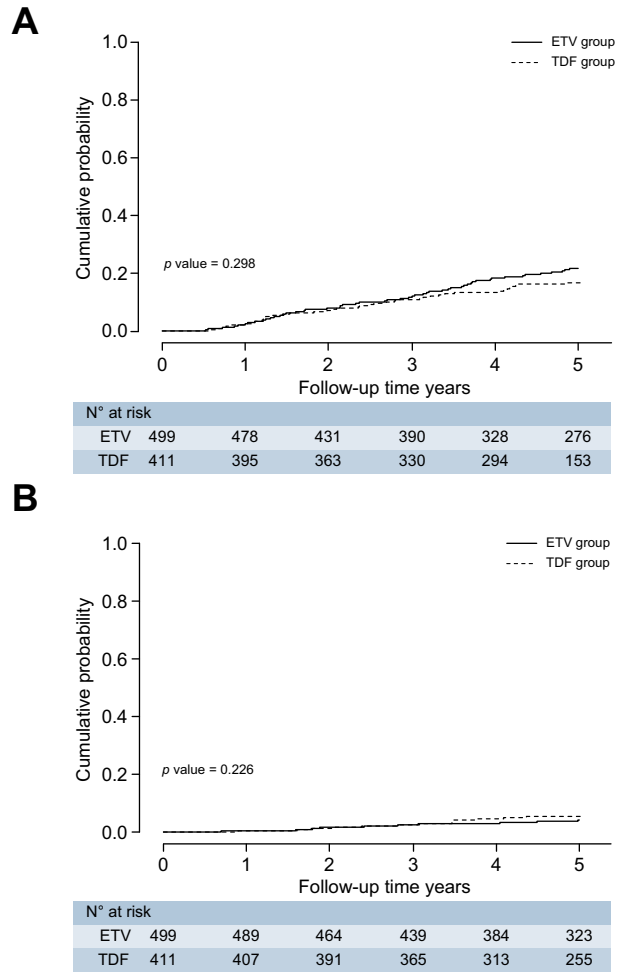

Fig. 3. Cumulative risk of HCC and death or OLT between ETV and TDF groups in patients with compensated cirrhosis. Kaplan-Meier curves of (A) HCC and (B) death or OLT in patients with compensated cirrhosis. ETV, entecavir; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplant; TDF, tenofovir disoproxil fumarate.

Table 3. Comparison of baseline characteristics between 2 groups among the patients with compensated cirrhosis.

Variables	ETV group (n = 499)	TDF group (n = 411)	*p* value
Age, years	52.6 ± 9.4	53.8 ± 10.2	0.074
Male gender	315 (63.1%)	279 (67.9%)	0.134
Presence of diabetes	62 (12.4%)	48 (11.7%)	0.731
Presence of hypertension	68 (13.6%)	56 (13.6%)	0.999
Body mass index, kg/m^2	24.0 ± 3.1	24.0 ± 3.2	0.945
Positive HBeAg	209 (41.9%)	150 (36.5%)	0.098
Log_{10} HBV-DNA, IU/ml	5.4 ± 1.9	5.4 ± 1.7	0.866
Prothrombin time, INR	1.0 ± 0.3	1.0 ± 0.4	0.403
Platelet counts, $\times 10^3/\mu l$	125.1 ± 61.8	125.8 ± 54.4	0.854
Bilirubin, mg/dl	0.88 ± 0.47	0.88 ± 0.46	0.820
Albumin, g/dl	3.97 ± 0.50	4.06 ± 0.47	0.004
Child-Pugh score	5.27 ± 0.52	5.19 ± 0.44	0.014
MELD score	8.42 ± 3.35	8.24 ± 3.14	0.414
Alpha-fetoprotein, ng/ml	13.7 ± 23.8	12.4 ± 23.1	0.437

Values are expressed as mean ± standard deviation or numbers (%).
*Calculated by Student's *t* test (or the Mann-Whitney *U* test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate)
ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio; MELD, model for end-stage liver disease; TDF, tenofovir disoproxil fumarate.

Table 4. Comparison of baseline characteristics between 2 groups after PS-matching and IPTW analysis among the patients with compensated cirrhosis.

	1:1 PS-matching analysis			IPTW analysis		
Variables	**ETV group**	**TDF group**	***p* value***	**ETV group**	**TDF group**	***p* value**
Age, years	53.5 ± 9.4	53.5 ± 9.9	0.943	53.1 ± 0.4	53.0 ± 0.5	0.891
Male gender	256 (67.4%)	256 (67.4%)	>0.999	331 (65.2%)	274 (64.9%)	0.927
Presence of diabetes	47 (12.4%)	43 (11.3%)	0.6374	62 (12.2%)	52 (12.4%)	0.933
Presence of hypertension	51 (13.4%)	48 (12.6%)	0.726	69 (13.6%)	57 (13.6%)	0.995
Body mass index, kg/m^2	23.98 ± 3.06	24.00 ± 3.06	0.928	24.03 ± 0.14	24.03 ± 0.17	0.997
Positive HBeAg	138 (36.3%)	145 (38.2%)	0.553	201 (39.6%)	169 (39.9%)	0.935
Log_{10} HBV-DNA, IU/ml	5.27 ± 1.91	5.39 ± 1.69	0.341	5.30 ± 0.09	5.45 ± 0.09	0.229
Prothrombin time, INR	0.98 ± 0.36	0.99 ± 0.36	0.828	1.01 ± 0.02	1.01 ± 0.02	0.969
Platelet counts, $\times 10^3/\mu l$	128.4 ± 63.9	124.9 ± 55.3	0.429	125.2 ± 2.7	125.1 ± 2.9	0.981
Bilirubin, mg/dl	0.86 ± 0.44	0.88 ± 0.47	0.543	0.88 ± 0.02	0.88 ± 0.02	0.982
Albumin, g/dl	4.04 ± 0.49	4.04 ± 0.47	0.952	4.01 ± 0.02	4.01 ± 0.03	0.917
Child-Pugh score	5.22 ± 0.48	5.20 ± 0.45	0.605	5.24 ± 0.02	5.23 ± 0.03	0.774
MELD score	8.09 ± 2.79	8.24 ± 3.17	0.526	8.35 ± 0.14	8.29 ± 0.16	0.790
Alpha-fetoprotein, ng/mL	19.21 ± 40.73	16.21 ± 34.53	0.250	18.31 ± 1.67	17.05 ± 1.91	0.620

Values are expressed as mean ± standard deviation or numbers (%).
*Calculated by paired *t* test or McNemar's test.
ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio; IPTW, inverse probability of treatment weighting; MELD, model for end-stage liver disease; PS, propensity score; TDF, tenofovir disoproxil fumarate.

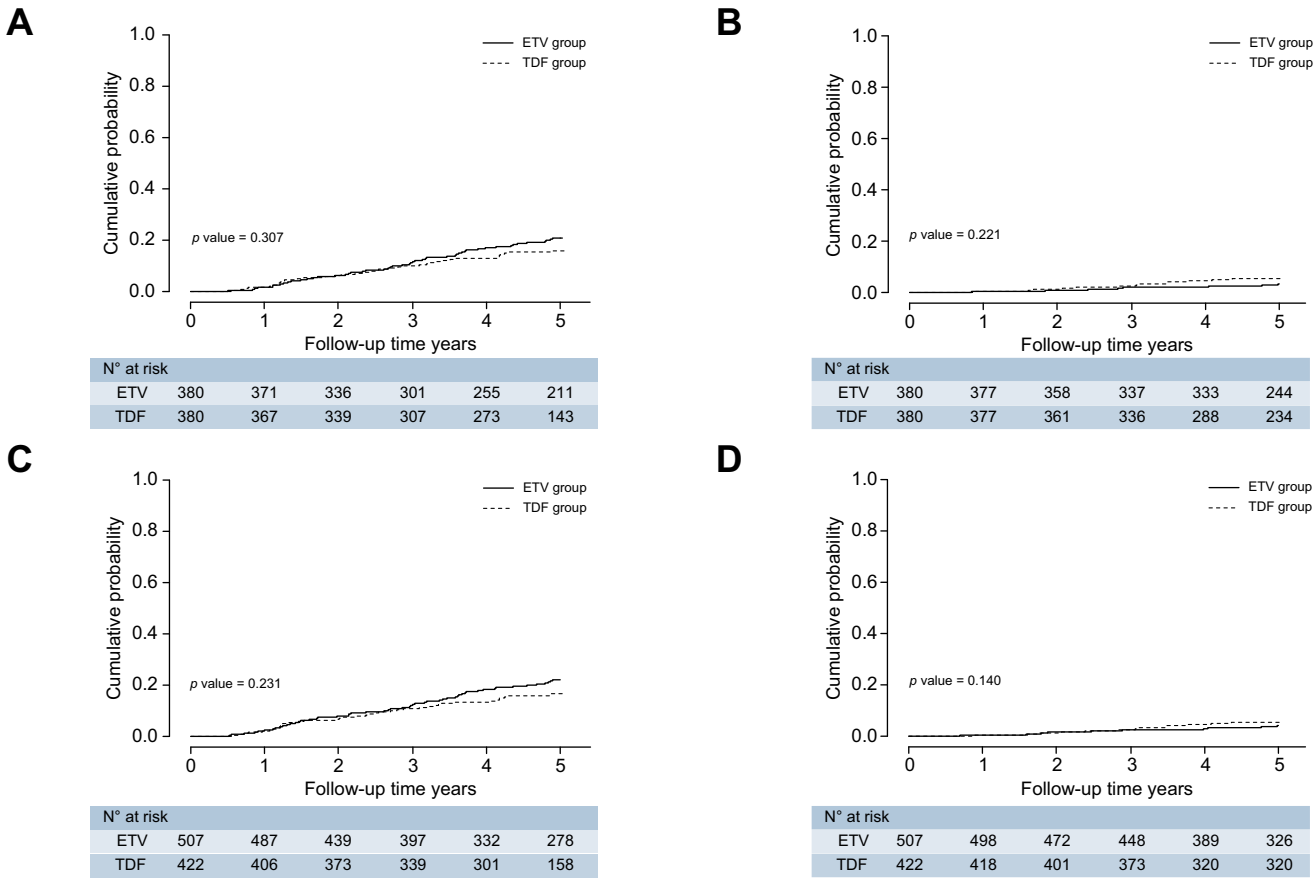

Fig. 4. Cumulative risk of HCC and death or OLT between ETV and TDF groups by PS-matching and IPTW analysis in patients with compensated cirrhosis. Kaplan-Meier curves of (A) HCC and (B) death or OLT by PS-matching analysis and of (C) HCC and (D) death or OLT by IPTW analysis among the patients with compensated cirrhosis. ETV, entecavir; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting; OLT, orthotopic liver transplant; PS, propensity score; TDF, tenofovir disoproxil fumarate.

Clinical outcomes among patients without cirrhosis

Among patients without cirrhosis (n = 1,987), a similar overall pattern of results was observed. The cumulative risk of HCC development at 1, 3, and 5 years was 0.2%, 1.0%, and 2.9%, respectively, in the ETV group; while it was 0.5%, 2.1%, and 3.8%, respectively, in the TDF group ($p = 0.078$), with an HR of 1.573 (95% CI 0.947–2.610; $p = 0.080$). By multivariate analysis, the risk of HCC was not statistically different between the 2 groups (adjusted HR 1.608; 95% CI 0.952–2.715; $p = 0.076$). The cumulative risk of death or OLT at 1, 3, and 5 years was 0.5%, 1.4%, and 1.8%, respectively, in the ETV group; while it was 0.2%, 1.0%, and 1.3%, respectively, in the TDF group

($p = 0.342$), with an HR of 0.701 (95% CI 0.336–1.464; $p = 0.344$). By multivariate analysis, the risk of death or OLT was not statistically different between the 2 groups (adjusted HR 0.888; 95% CI 0.415–1.901; $p = 0.761$).

Subgroup analyses according to other clinical parameters

In addition, we performed subgroup analyses when stratified according to baseline serum HBV-DNA level, age, risk scores, *i.e.* CAMD score and modified PAGE-B score.[24,25] Likewise, a similar overall pattern in the results was observed consistently (all $p > 0.05$). These clinical data are provided in Tables S2 and S3.

Discussion

The current guidelines for the treatment of patients with CHB recommend ETV, TDF, or (if appropriate) TAF, as the first-line antiviral therapy.[4,9,26] Of these, ETV and TDF have similar rates of HBV-DNA suppression and alanine aminotransferase normalization, as well as excellent safety profiles.[20] However, Choi *et al.* [21] reported that the risk of HCC development in TDF-treated patients should be ~35% lower than that in ETV-treated patients in an NHIS-based cohort (n = 24,156) and a tertiary hospital cohort (n = 2,701). Given the poor prognosis of HCC, determining the treatment of choice for patients with CHB could become a scientifically, socio-economically, and ethically important matter. We assessed this issue in an independent, large-scale, multicenter cohort study.

In multivariate, PS-matched, and IPTW analyses, the TDF group showed comparable clinical outcomes in terms of HCC and death or OLT compared to the ETV group (all $p > 0.05$). These results were reproduced in the patients with compensated cirrhosis. Our findings differ significantly from those of Choi *et al.* [21] in terms of the cumulative HCC risk during long-term NUC therapy. One of the possible explanations for such a discrepancy is a preference for ETV over TDF by some hepatologists for patients with CHB and unfavorable medical characteristics, such as old age, metabolic comorbidities associated with renal disease (*e.g.*, diabetes with or without hypertension), obesity, and smoking; these may contribute to HCC development.[27] As TDF was approved ~6 years later than ETV in South Korea, physicians were already aware of the potential safety issues associated with long-term TDF use in this population at the time of an official approval by the NHIS.[28] Furthermore, we could raise several major drawbacks of the article by Choi *et al.*[21] First of all, the frequency of regimen change in the ETV group in the hospital cohort of Choi *et al.*[21] was 11.7%, which is somewhat high given the resistance rate of <2.0% among treatment-naïve patients and the proven safety of long-term ETV therapy.[1,4,9,15,29] However, detailed reasons for the change (*e.g.* patient's preference, adverse effect, resistance mutation, or partial virologic response) remain unknown. Second, since the NHIS-based database includes age, gender, diagnosis code, and only reimbursed medications, a thorough and (if necessary) repeated review of the medical records was not feasible. This contrasts with our multicenter cohort which can reliably yield higher resolution data in terms of medication history, baseline clinical and laboratory data, on-treatment clinical courses, and HCC surveillance.

Our study has several strengths. First, the large sample of almost 2,900 patients drawn from 4 independent academic teaching hospitals enhanced the reliability of the results. Additionally, there were a sufficient number of HCC cases (n = 240, 8.3%) during the median follow-up period of 59.2 months to give adequate statistical power.[30] These results were consistently reproduced when stratified by each participating hospital (all $p > 0.05$; data not shown) and were also consistent with previous studies conducted in diverse populations in Europe, South Korea, and India.[11–14,31] However, so far, only 1 study on the basis of a single-hospital cohort has reported that TDF is marginally superior to ETV for reducing the risk of HCC.[21] Second, our hospital-based study provides additional data, allowing for a more thorough comparison. For example, the difference in complete virologic response rate (defined as serum HBV-DNA <60 IU/ml) between the ETV and TDF groups at 24 months was not statistically significant (86.5% *vs.* 87.5%, respectively; $p = 0.440$), and there was no significant difference in HCC incidence between those with complete virologic response and those without ($p = 0.831$). Besides, after recruiting patients who received entecavir 0.5 mg following previous exposure to lamivudine or telbivudine, we assessed their cumulative probability of HCC development and found that it was not statistically different to that in treatment-naïve patients who received entecavir 0.5 mg as a first-line antiviral agent ($p = 0.094$; data not shown). In a previous study assessing the HCC risk in patients treated with lamivudine or entecavir 0.5 mg in first-line, the overall risk of HCC was similar, provided that patients received timely and appropriate rescue therapy against virologic breakthrough or resistance mutations during the periodic follow-up.[32] Hence, we would like to emphasize the importance of careful monitoring in patients being treated with NUCs.

To support their conclusions, Choi *et al.*[21] hypothesized that ETV may have carcinogenic potential, while TDF may induce interferon (IFN)-λ3 production; however, their hypotheses are also problematic. First, ETV has been reported to increase the incidence of lung adenomas and carcinomas, HCC, and vascular tumors in mice at 4 mg/kg, as well as increasing the incidence of HCC, brain microglial tumors, and skin fibroma in rats at 1.4–2.6 mg/kg.[33] However, these dosages are at least 100-fold those used in humans. In contrast, 2 recent large-scale real-life studies[34,35] reported that long-term ETV therapy does not increase the risk of cancer. In addition, in the long-term follow-up study by Kim *et al.*,[36] the incidence of HCC was not statistically different during and after the first 5 years of ETV treatment (2.29% *vs.* 1.66%, $p = 0.22$). If long-term maintenance of ETV had a significant pro-carcinogenic effect on humans, the HCC incidence would have progressed rapidly with time. In addition, although IFN-λ3 production might be induced by long-term TDF therapy,[37] conflicting data have also been reported.[38–42] Because IFN-λ assays have not been standardized, neither its anti-carcinogenic effect in the human liver nor the causality of the relationship between a higher IFN-λ3 level and a lower incidence of HCC have been confirmed.

This study also had limitations. First, its retrospective design may introduce selection bias, particularly in terms of treatment allocation. To overcome this, we performed various statistical adjustments as well as subgroup analyses. Therefore, a prospective randomized study of the association between antiviral type and HCC risk is needed; however, such a study is unlikely to be conducted in the near future. Therefore, this observational study has considerable scientific value. Furthermore, because most (>98%) patients with CHB in South Korea become infected with genotype C HBV by vertical transmission,[1,43] our results may not be generalizable to the entire HBV-infected population. However, because the overall virologic response rates of NUCs are

similar among HBV genotypes, in contrast to pegylated IFN therapy,[1] our results will likely be reproduced in other countries. Last, since the NHIS, as a single payer in South Korea, provides health insurance to more than 99% of the whole population, some overlap might exist between the NHIS database and our multicenter cohort database. However, our study may have an advantage in that we can provide more comprehensive and reliable results than the NHIS database, where only limited data are available. In addition, as the conclusions of several studies[12,21,31] have been contradictory, it is important that the fundamental differences between the studies are determined.

In conclusion, the overall prognosis in terms of development of HCC and death or OLT was not statistically different between patients treated with ETV versus TDF. Because prevention of liver-disease progression by appropriate antiviral therapy is a very important medical and socio-economical issue, further studies are needed to validate our results.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conception and design: B.K. Kim, S.Y. Park, Y.S. Seo, S.U. Kim; Development of methodology: B.K. Kim, S.Y. Park, Y.S. Seo, S.U. Kim; Acquisition, analysis and interpretation of data: B.K. Kim, S.Y. Park, H.A. Lee, Y.S. Seo, S.U. Kim; Writing, review, and/or revision of the manuscript: B.K. Kim, S.Y. Park, M.N. Lee, H.A. Lee, H. W. Lee, J.Y. Park, D.Y. Kim, S.H. Ahn, K.H. Han, S.G. Hwang, K.S. Rim, Soon Ho Um, W.Y. Tak, Y.O. Kweon, Y.S. Seo, S.U. Kim; Administrative, technical, or material support: B.K. Kim, S.Y. Park, Y.S. Seo, S.U. Kim; Study supervision: B.K. Kim, S.Y. Park, Y.S. Seo, S.U

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Supplementary data

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