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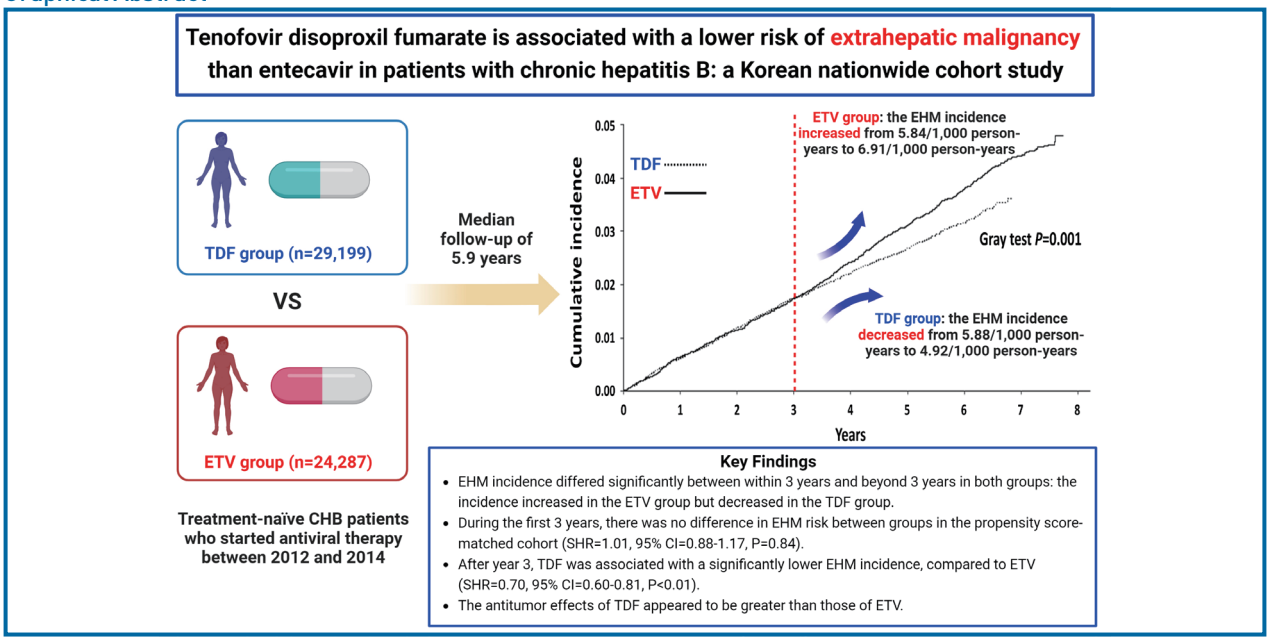
Original Article

Extrahepatic malignancies and antiviral drugs for chronic hepatitis B: A nationwide cohort study

Moon Haeng Hur[1,*], Dong Hyeon Lee[1,2,*], Jeong-Hoon Lee[1,3], Mi-Sook Kim[4], Jeayeon Park[1], Hyunjae Shin[1], Sung Won Chung[1], Hee Jin Cho[1], Min Kyung Park[1], Heejoon Jang[2], Yun Bin Lee[1], Su Jong Yu[1], Sang Hyub Lee[1], Yong Jin Jung[2], Yoon Jun Kim[1], and Jung-Hwan Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine; [2]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea; [3]Genome Insight Inc., San Diego, CA, USA; [4]Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Korea

Graphical Abstract



Study Highlights

- In both the ETV and TDF groups, EHM incidence changed significantly between within 3 years and beyond 3 years: the incidence increased in the ETV group, whereas it decreased in the TDF group.
- During the first 3 years, the incidence of EHM was comparable between the two groups. After year 3, however, TDF was associated with a significantly lower risk of EHM than ETV.
- Regarding intrahepatic malignancy, the superiority of TDF over ETV was observed both before year 3 and after year 3, with the latter being more prominent.

Background/Aims: Chronic hepatitis B (CHB) is related to an increased risk of extrahepatic malignancy (EHM), and antiviral treatment is associated with an incidence of EHM comparable to controls. We compared the risks of EHM and intrahepatic malignancy (IHM) between entecavir (ETV) and tenofovir disoproxil fumarate (TDF) treatment.

Methods: Using data from the National Health Insurance Service of Korea, this nationwide cohort study included treatment-naïve CHB patients who initiated ETV (n=24,287) or TDF (n=29,199) therapy between 2012 and 2014. The primary outcome was the development of any primary EHM. Secondary outcomes included overall IHM development. E-value was calculated to assess the robustness of results to unmeasured confounders.

Results: The median follow-up duration was 5.9 years, and all baseline characteristics were well balanced after propensity score matching. EHM incidence rate differed significantly between within versus beyond 3 years in both groups (P<0.01, Davies test). During the first 3 years, EHM risk was comparable in the propensity score-matched cohort (5.88 versus 5.84/1,000 person-years; subdistribution hazard ratio [SHR]=1.01, 95% confidence interval [CI]=0.88–1.17, P=0.84). After year 3, however, TDF was associated with a significantly lower EHM incidence compared to ETV (4.92 versus 6.91/1,000 person-years; SHR=0.70, 95% CI=0.60–0.81, P<0.01; E-value for SHR=2.21). Regarding IHM, the superiority of TDF over ETV was maintained both within (17.58 versus 20.19/1,000 person-years; SHR=0.88, 95% CI=0.81–0.95, P<0.01) and after year 3 (11.45 versus 16.20/1,000 person-years; SHR=0.68, 95% CI=0.62–0.75, P<0.01; E-value for SHR=2.30).

Conclusions: TDF was associated with approximately 30% lower risks of both EHM and IHM than ETV in CHB patients after 3 years of antiviral therapy. **(Clin Mol Hepatol 2024;30:500-514)**

Keywords: Non-liver cancer; Hepatitis B virus; Antiviral treatment; Tenofovir; Entecavir

INTRODUCTION

Chronic hepatitis B (CHB) infection is the most prevalent chronic viral infection worldwide, affecting more than 250 million people and accounting for approximately 45% of hepatocellular carcinoma (HCC) cases.[1,2] Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have been the most commonly used nucleos(t)ide-analogues (NAs) for CHB patients and both are currently recommended as first-line antivirals because of their high potency and genetic barrier against the development of NA resistance.[3-5]

It remains controversial which of the two antivirals, ETV or TDF, is superior for the prevention of HCC in CHB patients.[6] While some cohort studies and meta-analyses have shown a lower risk of HCC in CHB patients treated with TDF,[7-10] other studies have demonstrated no significant differences between the two antivirals.[11-15] However, no study has proved the superiority of ETV over TDF. It has been

Corresponding author : **Jeong-Hoon Lee**
Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2228, Fax: +82-2-743-6701, E-mail: pindra@empal.com
https://orcid.org/0000-0002-0315-2080

*These two authors equally contributed to this study as co-first authors.

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Abbreviations:

CHB, chronic hepatitis B; EHM, extrahepatic malignancy; IHM, intrahepatic malignancy; ETV, entecavir; TDF, tenofovir disoproxil fumarate; SHR, subdistribution hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; NAs, nucleos(t)ide-analogues; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; HBV, hepatitis B virus

suggested that more effective and earlier viral suppression with TDF may lead to better outcomes.[7] Some researchers suspect that the protumor or carcinogenic effects of ETV reported in a preclinical animal model[16] might be responsible for the inferiority of ETV, but none of these effects have not been confirmed in humans.[17,18]

Meanwhile, our group recently reported that patients with CHB have a higher risk of developing a primary extrahepatic malignancy (EHM) than controls.[19] Furthermore, we demonstrated that complete viral suppression with long-term NA treatment was associated with a lower risk of EHM among CHB patients. There has been no study comparing ETV and TDF in terms of EHM prevention. Therefore, we aimed to compare the risk of EHM as well as intrahepatic malignancy (IHM) between patients treated with ETV and those treated with TDF; the results may reflect the antitumor or protumor effects of each antiviral.

MATERIALS AND METHODS

Data source

We established a retrospective cohort using nationwide claims in the National Health Insurance Service (NHIS) database of South Korea. NHIS is a health insurance policy that covers 97% of South Koreans; its utility for research purposes has been well-established.[20] The NHIS database uses the tenth revision of the International Classification of Diseases (ICD-10). The Institutional Review Boards of both the NHIS (No. NHIS-2021-1-804) and SMG–SNU Boramae Medical Center (No. 07-2019-23) approved this study. The requirement for informed consent was waived due to the retrospective nature of this study and because patient data within the NHIS database is coded anonymously.

Study populations and variables

The study cohort originally included 178,937 patients with CHB who initiated treatment with ETV or TDF between January 1, 2012 and December 31, 2014. The cohort entry date and index date were defined as the first day of NA treatment and the 90th day after initiating NA therapy, respectively. After applying exclusion criteria, the final study population included 53,486 patients with CHB (24,287 received ETV [ETV group] and 29,199 received TDF [TDF group]; Fig. 1). For each subject, we obtained demographic information, comorbidity data, and NA data, including the type and cumulative defined daily dose of antiviral used. The presence of liver cirrhosis and/or decompensation was identified using ICD-10 diagnosis codes, NHIS classification codes for specific procedures (e.g., abdominal paracentesis and endoscopic treatment of esophageal or gastric varices), and relevant prescriptions. Supplementary Table 1 shows the diagnosis, procedural, and prescription codes used in this study. In the subset of individuals who received health check-ups provided by the NHIS, anthropometric data, blood test results, and health-related behaviors (smoking, alcohol intake, and physical activity) were also collected. Further details regarding the study population are described in the Supplementary Methods.

Outcomes

The primary outcome was the development of any EHM. EHMs were defined according to ICD-10 codes for non-liver cancers, as well as cancer-specific insurance claim codes. Only the first diagnosed malignancy after the index date was counted as an event. Death and a new IHM were considered competing events. Secondary outcomes were the development of specific EHMs (the 10 most prevalent EHMs in South Korea) and overall IHM. The date of the first claim with the ICD-10 code was considered the date of cancer diagnosis. Further information is provided in the Supplementary Methods.

Statistical analysis

To compare categorical and continuous variables, the standardized difference was measured between the two groups. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were employed to balance the ETV and TDF groups; propensity scores were calculated using all covariates. Study subjects were followed from the index date to the date of EHM diagnosis, date of any competing event, or cut-off date (December 31, 2019), whichever occurred first. The log-log plot and Schoenfeld residual test were utilized to validate the proportional hazards assumption inside the Cox model. If the proportional hazards assumption was not satisfied, an ex-

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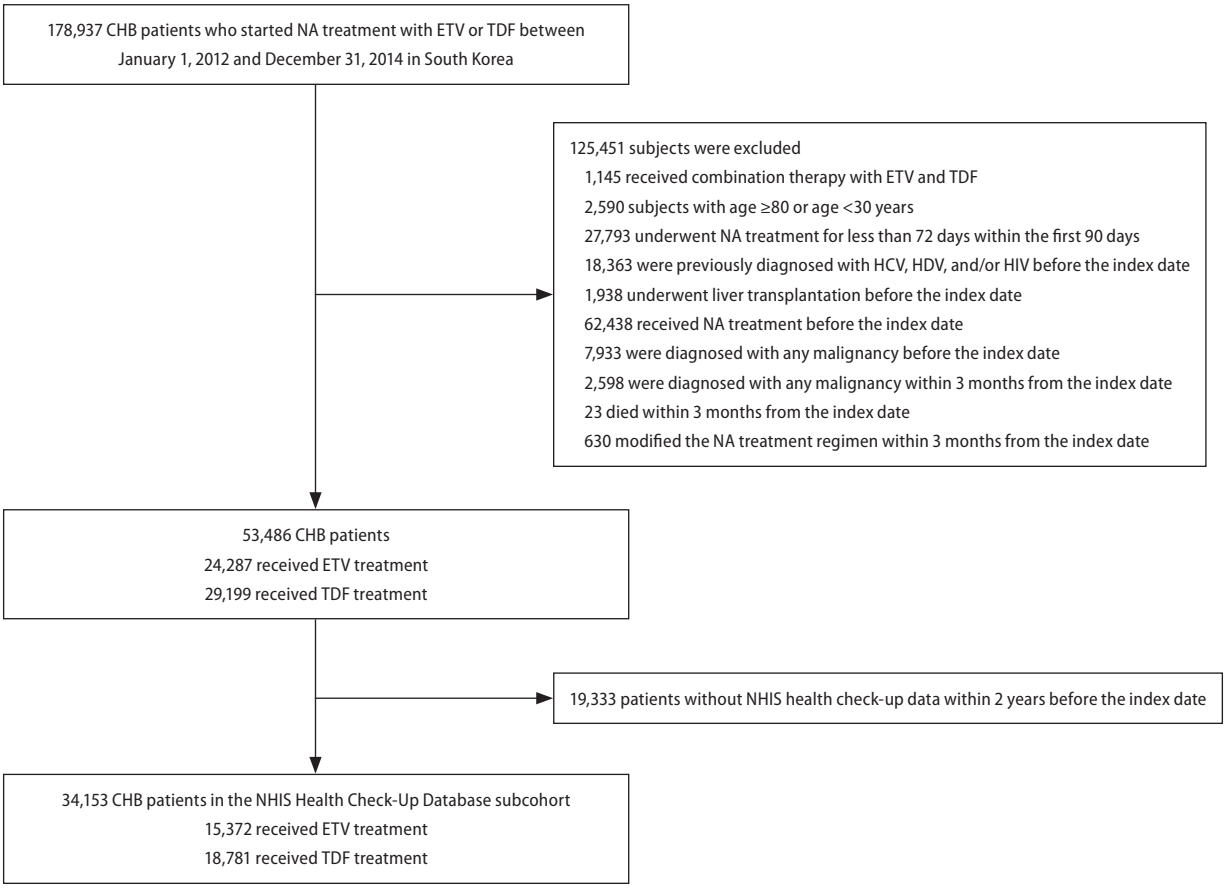

Figure 1. Patient flow diagram. Specific diagnostic and procedural codes are presented in Supplementary Table 1. CHB, chronic hepatitis B; ETV, entecavir; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; NA, nucleos(t)ide-analogue; NHIS, National Health Insurance Service; TDF, tenofovir disoproxil fumarate.

tended Cox model with Heaviside functions was used.

Cumulative incidence of EHM was derived using the cumulative incidence function, and cumulative incidence curves were compared using the Gray test. Applying segmented linear regression, the cumulative incidence was fitted as a piecewise linear function, and change in slope was assessed using the Davies test. To estimate the effect of variables on the cumulative incidence, while taking competing events into account, we used the Fine–Gray model to calculate the subdistribution hazard ratio (SHR). *P*-value for interaction ($P_{interaction}$) was calculated to assess whether NA therapy had differential impacts on EHMs according to subgroups. Various sensitivity analyses were performed to confirm the robustness of our findings (see Supplementary Methods). E-value was calculated to estimate the magnitude of an unadjusted confounding variable needed to mitigate the association between antiviral treatment and the incidence of EHM or IHM.[21] All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc, Cary, NC, USA) and R 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). *P*-values were derived from two-tailed tests, with values <0.05 considered statistically significant.

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of the ETV and TDF groups. Although the healthcare level differed slightly between groups in the crude population, all variables, including age, sex, and coexisting medical conditions, were well balanced after PSM or IPTW. Baseline

Table 1. Baseline characteristics of the study cohort before and after propensity score matching or inverse probability of treatment weighting

Characteristics	Unmatched cohort			After propensity score matching*			After inverse probability of treatment weighting *		
	ETV (n=24,287)	TDF (n=29,199)	Standardized difference	ETV (n=24,285)	TDF (n=24,285)	Standardized difference	ETV (n=23,664)	TDF (n=28,559)	Standardized difference
Age, years	48.6±10.3	48.3±10.3	0.03	48.6±10.3	48.5±10.2	0.02	48.4±10.2	48.4±10.3	<0.01
Sex			0.02			0.01			<0.01
Male	15,664 (64.5)	18,523 (63.4)		15,664 (64.5)	15,582 (64.2)		15,193 (64.2)	18,330 (64.2)	
Female	8,623 (35.5)	10,676 (36.6)		8,621 (35.5)	8,703 (35.8)		8,471 (35.8)	10,229 (35.8)	
Socioeconomic status†									
High	7,965 (32.8)	10,290 (35.2)	−0.05	7,964 (32.8)	8,149 (33.6)	−0.02	8,003 (33.8)	9,721 (34.1)	<0.01
Middle	10,941 (45.1)	13,025 (44.6)	0.01	10,940 (45.1)	11,016 (45.3)	−0.01	10,747 (45.4)	12,940 (45.3)	<0.01
Low	3,880 (16.0)	4,443 (15.2)	0.02	3,880 (16.0)	3,805 (15.7)	0.01	3,719 (15.7)	4,462 (15.6)	<0.01
Medical aid	837 (3.4)	753 (2.6)	0.05	837 (3.4)	714 (2.9)	0.03	596 (2.5)	719 (2.5)	<0.01
Others‡	664 (2.7)	688 (2.4)	0.02	664 (2.7)	601 (2.5)	0.02	599 (2.6)	717 (2.5)	<0.01
Level of healthcare									
Tertiary	6,663 (27.4)	10,067 (34.5)	−0.15	6,661 (27.4)	6,620 (27.3)	<0.01	7,280 (30.8)	8,855 (31.0)	<0.01
Secondary	11,299 (46.5)	11,240 (38.5)	0.16	11,299 (46.5)	11,155 (45.9)	0.01	9,943 (42.0)	11,938 (41.8)	<0.01
Primary	6,325 (26.1)	7,892 (27.0)	−0.02	6,325 (26.1)	6,510 (26.8)	−0.02	6,441 (27.2)	7,766 (27.2)	<0.01
Coexisting medical conditions									
Cirrhosis	6,737 (27.7)	8,302 (28.4)	−0.02	6,736 (27.7)	6,722 (27.7)	<0.01	6,332 (26.8)	7,658 (26.8)	<0.01
Decompensated cirrhosis	2,129 (8.8)	2,151 (7.4)	0.05	2,129 (8.8)	1,944 (8.0)	0.03	1,711 (7.2)	2,016 (7.1)	0.01
Ascites	987 (4.1)	913 (3.1)	0.05	987 (4.1)	863 (3.6)	0.03	669 (2.8)	757 (2.7)	0.01
Varices	1,441 (5.9)	1,524 (5.2)	0.03	1,441 (5.9)	1,343 (5.5)	0.02	1,261 (5.3)	1,517 (5.3)	<0.01
Diabetes mellitus	4,571 (18.8)	5,124 (17.6)	0.03	4,570 (18.8)	4,376 (18.0)	0.02	4,250 (18.0)	5,112 (17.9)	<0.01
Hypertension	5,480 (22.6)	6,323 (21.7)	0.02	5,478 (22.6)	5,314 (21.9)	0.02	5,164 (21.8)	6,241 (21.8)	<0.01
CCI§point	1.2±1.4	1.2±1.3	−0.01	1.2±1.4	1.2±1.3	0.02	1.2±1.3	1.2±1.2	0.01

Data are expressed as number (%) or mean±standard deviation.
CCI, Charlson Comorbidity Index; ETV, entecavir; TDF, tenofovir disoproxil fumarate.
*Propensity scores were computed using following variables: age, sex, socioeconomic status, level of healthcare, cirrhosis, decompensated cirrhosis, ascites, varices, diabetes mellitus, hypertension, and Charlson Comorbidity Index. †High, middle, and low socioeconomic statuses indicate socioeconomic status within the ≥75th, 25th–75th, and <25th percentiles, respectively. ‡Patients with a special occupation such as military personnel or shipping labor union. §Charlson Comorbidity Index was based on data from 1 year before the cohort entry date.

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characteristics of the NHIS Health Check-Up Database subcohort are summarized in Supplementary Table 2. Additional anthropometric, habitual, and laboratory variables were well balanced. Distributions of propensity scores for both the entire study population and the NHIS Health Check-Up Database subcohort showed good concordance between treatment groups, without extreme values (Supplementary Fig. 1).

Incidence of primary extrahepatic malignancies

Median follow-up durations of the ETV and TDF groups were 6.3 years (interquartile range [IQR]=3.7–7.2 years) and 5.7 years (IQR=5.1–6.4 years), respectively (Table 2). After PSM, there were 822 (3.4%) EHMs in the ETV group and 706 (2.9%) EHMs in the TDF group.

Figure 2 shows the cumulative incidence of primary EHM after PSM. During the entire study period, TDF was associated with a lower risk of EHM than ETV (P=0.001 by Gray test). Differences in risk of EHM between groups became more prominent after 3 years from the index date. The incidence rate of EHM decreased in the TDF group but increased in the ETV group after year 3 (both P<0.01 by Davies test; Supplementary Fig. 2). In the TDF group, the crude incidence of EHM decreased from 5.88/1,000 person-years in the first 3 years to 4.92/1,000 person-years after year 3 (Table 2). Conversely, in the ETV group, the incidence of EHM increased from 5.84/1,000 person-years in the first 3 years to 6.91/1,000 person-years after year 3.

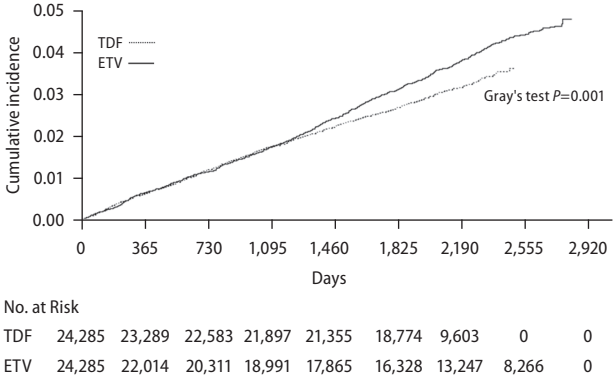

Figure 2. Cumulative incidence of extrahepatic malignancies in propensity score-matched cohort. Analysis was performed after propensity score matching. Intrahepatic malignancy development and death were treated as competing events. ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Table 2. Clinical outcomes in propensity score-matched cohort of chronic hepatitis B patients treated with entecavir or tenofovir disoproxil fumarate

	cDDDs (per patient per year)	Events, no. (%)	Median follow-up, year (IQR)	Crude incidence of extrahepatic malignancy, per 1000 person-year		Within 3 years		After 3 years	
				Within 3 years	After 3 years	SHR (95% CI)	*P*-value	SHR (95% CI)	*P*-value
ETV	288.4	822 (3.4%)	6.3 (3.7–7.2)	5.84 (5.28–6.46)	6.91 (6.30–7.58)	[reference]		[reference]	
TDF	293.4	706 (2.9%)	5.7 (5.1–6.4)	5.88 (5.33–6.48)	4.92 (4.40–5.51)	1.01 (0.88–1.17)	0.84	0.70 (0.60–0.81)	<0.01

cDDDs, cumulative defined daily doses; CI, confidence interval; ETV, entecavir; IQR, interquartile range; NA, nucleos(t)ide analogue; SHR, subdistribution hazard ratio; TDF, tenofovir disoproxil fumarate.

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According to the Schoenfeld residual test, the Cox proportional hazards assumption was satisfied if the study period was divided as within 3 years and after 3 years from the index date (P=0.82) but not if the entire study period was considered (P<0.01). The log-log plot reproduced these results (Supplementary Fig. 3). Thus, we stratified the study duration into within the first 3 years and beyond the first 3 years in all analyses and applied the extended Cox model.

EHM incidence within the first 3 years did not differ between antivirals (TDF vs. ETV: SHR=1.01, 95% confidence interval [CI]=0.88–1.17, P=0.84), whereas the risk of EHM was significantly lower in the TDF group than in the ETV group after year 3 (SHR=0.70, 95% CI=0.60–0.81, P<0.01). Similar results were obtained in most subgroup analyses (age, socioeconomic status, and other medical conditions; all $P_{interaction}$>0.05) except sex (Fig. 3). E-value analysis showed that an unexplained confounder would need to be associated with both NA type and EHM incidence at a risk ratio of 2.21 to mitigate the relationship between these variables and make the SHR=1, while controlling for other covariates in our model (Supplementary Table 3).

Sensitivity analyses

Various sensitivity analyses showed similar results (Table 3 and Supplementary Results). The main result was maintained in the study population balanced using IPTW (SHR=0.70, 95% CI=0.61–0.81, P<0.01). Supplementary

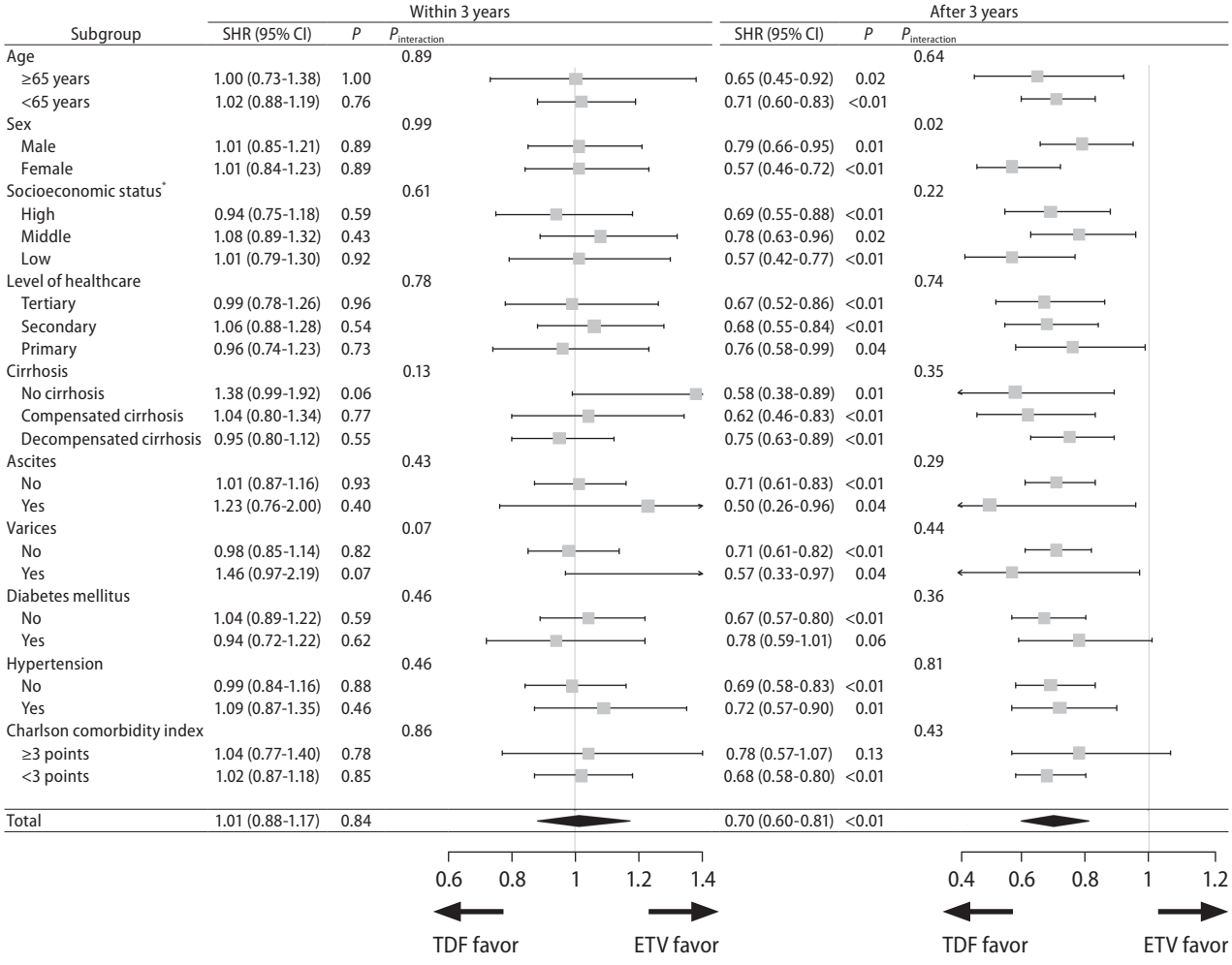

Figure 3. Risk of extrahepatic malignancy in the propensity score-matched cohort according to prespecified subgroups. SHR, subdistribution hazard ratio; CI, confidence interval; ETV, entecavir; $P_{interaction}$, P-value for interaction; TDF, tenofovir disoproxil fumarate. *High, middle, and low socioeconomic statuses indicate socioeconomic status within the ≥75th, 25th–75th, and <25th percentiles, respectively.

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Figure 4 presents the cumulative incidence of primary EHMs in both treatment groups before and after IPTW. Similar to the analysis of the study population balanced using PSM, the difference in EHM incidence between groups became more apparent after year 3. The superiority of TDF over ETV was also reproduced when analyzing the NHIS Health Check-Up Database subcohort (SHR=0.68, 95% CI=0.57–0.83, *P*<0.01). In this subcohort, the cumulative incidence of EHM differed significantly between groups (Supplementary Fig. 4). In subgroup analyses of the NHIS Health Check-Up Database subcohort, most subgroups had a $P_{interaction}$>0.05, except for sex and presence of cirrhosis subgroups (Supplementary Fig. 5).

Incidence of specific extrahepatic malignancies

Supplementary Table 4 shows the incidence of specific EHM and IHM after PSM. After year 3, TDF was associated with a significantly lower risk of stomach cancer (SHR=0.57, 95% CI=0.38–0.86, *P*=0.01), breast cancer (SHR=0.53, 95% CI=0.33–0.85, *P*=0.01), and non-Hodgkin lymphoma (SHR=0.34, 95% CI=0.15–0.78, *P*=0.01) than ETV. Within the first 3 years, TDF was associated with a higher incidence of breast cancer than ETV (SHR=1.74, 95% CI=1.05–2.89, *P*=0.03).

Incidence of overall intrahepatic malignancies

Supplementary Figure 6 depicts the cumulative incidence of primary IHM in the entire population and the NHIS Health Check-Up Database subcohort after PSM. Similar to EHM, differences in IHM risk between groups became more prominent after approximately 3 years from the index date. However, unlike EHMs, the annual incidence rate of IHM decreased in the ETV group as well as the TDF group after year 3 (*P*<0.01 by Davies test; Supplementary Fig. 7). In the ETV group, the incidence of IHM decreased from 20.19/1,000 person-years to 16.20/1,000 person-years after year 3 (Supplementary Table 4). In the TDF group, the crude incidence of IHM decreased from 17.58/1,000 person-years in the first 3 years to 11.45/1,000 person-years after year 3. In terms of IHM incidence, the superiority of TDF over ETV was confirmed both within 3 years (SHR=0.88, 95% CI=0.81–0.95, *P*<0.01) and after 3 years (SHR=0.68, 95% CI=0.62–0.75, *P*<0.01), with the differ-

Table 3. Results of sensitivity analyses

	cDDDs (per patient per year)	Events, no. (%)	Median follow-up, year (IQR)	Crude incidence of extrahepatic malignancy, per 1000 person-year		Within 3 years			After 3 years			
				Within 3 years	After 3 years	SHR (95% CI)	*P*-value	aSHR (95% CI)	SHR (95% CI)	*P*-value	aSHR (95% CI)	*P*-value
Analyses to minimize detection bias												
Model 1A: Hospital visit-adjusted[*†]												
ETV	288.2	711 (3.2%)	6.5 (4.8–7.3)	4.14 (3.67–4.68)	6.91 (6.30–7.58)	[reference]			[reference]			
TDF	293.3	591 (2.5%)	5.8 (5.1–6.4)	4.23 (3.77–4.74)	4.92 (4.40–5.51)	1.02 (0.87–1.21)	0.78		0.71 (0.61–0.82)	<0.01		
Model 1B: Surveillance-adjusted[*‡]												
ETV	288.2	711 (3.2%)	6.5 (4.8–7.3)	4.14 (3.67–4.68)	6.91 (6.30–7.58)	[reference]			[reference]			

Table 3. Continued

	cDDDs (per patient per year)	Events, no. (%)	Median follow-up, year (IQR)	Crude incidence of extrahepatic malignancy, per 1000 person-year		Within 3 years				After 3 years			
				Within 3 years	After 3 years	SHR (95% CI)	*P*-value	aSHR (95% CI)	*P*-value	SHR (95% CI)	*P*-value	aSHR (95% CI)	*P*-value
TDF	293.3	591 (2.5%)	5.8 (5.1–6.4)	4.23 (3.77–4.74)	4.92 (4.40–5.51)	1.00 (0.84–1.18)	0.97			0.68 (0.59–0.79)	<0.01		
Different statistical approaches													
Model 2A: Cause-specific analysis[‡,§]													
ETV	288.4	822 (3.4%)	6.3 (3.7–7.2)	5.84 (5.28–6.46)	6.91 (6.30–7.58)	[reference]				[reference]			
TDF	293.4	706 (2.9%)	5.7 (5.1–6.4)	5.88 (5.33–6.48)	4.92 (4.40–5.51)	1.01 (0.88–1.16)	0.90			0.69 (0.60–0.81)	<0.01		
Model 2B: After IPTW													
ETV	288.3	794 (3.4%)	6.4 (3.7–7.2)	5.78 (5.21–6.41)	6.80 (6.19–7.47)	[reference]				[reference]			
TDF	293.9	812 (2.8%)	5.7 (5.1–6.4)	5.62 (5.13–6.16)	4.92 (4.43–5.46)	0.98 (0.85–1.12)	0.76			0.70 (0.61–0.81)	<0.01		
Model 3: NHIS Health Check-Up Database[*]													
ETV	296.5	525 (3.4%)	6.3 (3.8–7.2)	6.05 (5.34–6.85)	6.78 (6.03–7.62)	[reference]				[reference]			
TDF	299.5	427 (2.8%)	5.8 (5.1–6.4)	5.58 (4.92–6.33)	4.73 (4.09–5.47)	0.93 (0.78–1.11)	0.41			0.68 (0.57–0.83)	<0.01		
Model 4: Without window period (including events within initial 3 months)[*,‖]													
ETV	289.8	822 (3.2%)	6.5 (3.4–7.4)	5.08 (4.57–5.65)	6.66 (6.09–7.28)	[reference]		[reference]		[reference]		[reference]	
TDF	295.0	829 (2.7%)	6.0 (5.3–6.6)	4.99 (4.54–5.49)	4.83 (4.38–5.33)	0.98 (0.85–1.13)	0.83	0.98 (0.85–1.13)	0.79	0.71 (0.62–0.82)	<0.01	0.71 (0.62–0.81)	<0.01
Model 5: Crude population[‖]													
ETV	288.4	822 (3.4%)	6.3 (3.7–7.2)	5.84 (5.28–6.46)	6.91 (6.30–7.58)	[reference]		[reference]		[reference]		[reference]	
TDF	294.0	829 (2.8%)	5.8 (5.1–6.4)	5.59 (5.10–6.12)	4.94 (4.46–5.48)	0.96 (0.84–1.11)	0.61	0.97 (0.84–1.11)	0.63	0.70 (0.61–0.81)	<0.01	0.70 (0.61–0.81)	<0.01

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Table 3. Continued

	cDDDs (per patient per year)	Events, no. (%)	Median follow-up, year (IQR)	Crude incidence of extrahepatic malignancy, per 1000 person-year		Within 3 years			After 3 years			
				Within 3 years	After 3 years	SHR (95% CI)	*P*-value	aSHR (95% CI)	*P*-value	SHR (95% CI)	*P*-value	aSHR (95% CI)	*P*-value
Model 6: Treatment initiation between 2013–2014[*]													
ETV	288.2	250 (3.3%)	5.5 (4.4–6.2)	5.81 (4.86–6.95)	7.77 (6.54–9.23)	[reference]				[reference]			
TDF	293.9	232 (3.0%)	5.7 (5.0–6.3)	6.07 (5.12–7.20)	5.24 (4.31–6.39)	1.05 (0.82–1.34)	0.70			0.69 (0.53–0.90)	0.01		

aSHR, adjusted subdistribution hazard ratio; cDDDs, cumulative defined daily doses; CI, confidence interval; ETV, entecavir; IPTW, inverse probability of treatment weighting; IQR, interquartile range; SHR, subdistribution hazard ratio; TDF, tenofovir disoproxil fumarate.
[*]Propensity score-matched cohort. [†]Additionally adjusted for the frequency of hospital visits. [‡]Further adjusted for the frequency of surveillance test (alpha-fetoprotein, abdominal ultrasonography, or contrast-enhanced computed tomography). [§]Hazard ratios (instead of subdistribution hazard ratios) are provided for model 2A. [||]Adjusted for the level of healthcare.

ence being more prominent after 3 years. According to the E-values for the IHM incidence, it seems less likely that there is an unmeasured confounder that could alter the superiority of TDF (Supplementary Table 3).

DISCUSSION

In this nationwide cohort study, CHB patients treated with TDF had a 30% lower risk of EHM than those treated with ETV after 3 years of antiviral therapy. During the first 3 years, the incidence of EHM did not differ between ETV and TDF groups. After year 3, however, EHM risk differed significantly between groups as the incidence of EHM accelerated in the ETV group but decelerated in the TDF group. These results were consistent across various sensitivity and subgroup analyses. Regarding IHMs, the superiority of TDF over ETV was observed during the entire study period, although the difference in IHM risk between groups also became more prominent after year 3. These findings collectively suggest the superiority of TDF over ETV in terms of both EHM and IHM prevention.

Superior virologic response of TDF compared to ETV might be responsible for the outcomes of this study. Although head-to-head clinical trials are limited, prior studies showed that TDF suppressed viral RNA,[22,23] as well as DNA,[7,24-27] more potently than ETV, and this suppression was associated with a reduced risk of HCC. Recent studies reported associations between hepatitis B virus (HBV) infection and the development of EHM,[19,28-30] and chronic inflammation in HBV-infected extrahepatic tissues.[31,32] TDF might lower viral load below a certain threshold level more rapidly than ETV, resulting in decreased local inflammation and subsequent malignant transformation. Interferon lambda 3 induced by nucleotide analogues (e.g., TDF and adefovir), but not by nucleoside analogues (e.g., ETV and lamivudine), may also contribute to the antitumor effects of TDF.[33] As interferon lambda exhibited potent antitumor effects in animal malignancy models,[34,35] this could provide another explanation for the superiority of TDF over ETV.

In this study, we used several statistical strategies to overcome the limitations of a retrospective design. The E-value represents the minimum strength of association that an unmeasured confounder must have with both the treatment and outcome to completely explain away a given

treatment–outcome association.[21] Based on the calculated E-value for the EHM incidence, the observed SHR of 0.70 could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 2.21-fold each, above and beyond the measured confounders, which seems unfeasible. Most of the general risk factors for EHM, including age, sex, and comorbidity, were well balanced in both the entire cohort and the NHIS Health Check-Up subcohort, even before matching. In addition, the distribution of several disease-specific risk factors was similar between the two groups. For instance, *Helicobacter pylori* infection is a main cause of stomach cancer, which is still prevalent in Korea, and its risk factors, including elevated cholesterol, male gender, old age, and low socioeconomic status, were comparable.[36] The risk factors for non-Hodgkin lymphoma (e.g., obesity, low physical activity, smoking, and alcohol intake) were well balanced between the two groups,[37,38] and the superiority of TDF was maintained after adjusting for surveillance intensity, a crucial factor in the diagnosis of thyroid cancer.[39] Considering the E-value for the IHM incidence, the superiority of TDF with respect to IHM risk is also unlikely to be overturned by unmeasured confounders, as baseline characteristics are evenly distributed between the two groups, including the proportion of liver cirrhosis, one of the most important risk factors for IHM. To minimize the effects of residual confounders, we also applied other statistical strategies, such as PSM, IPTW, multivariable adjustment, and various prespecified sensitivity and subgroup analyses, which produced similar results.

The lower incidence of both EHM and IHM in the TDF group compared to the ETV group became more prominent after year 3. This suggests that antitumor effects of antivirals may require a certain period of time to manifest as differences in EHM or IHM incidence. However, IHM incidence was also significantly different within the first 3 years as well, although EHM incidence was comparable between groups during this time. Since HBV is a hepatotropic virus, the viral load is much higher in the liver than in extrahepatic tissues; thus, differences in antitumor effects resulting from different efficacy of viral suppression may be more apparent when comparing the incidence of IHM, rather than EHM. The further decrease in incidence of IHM after year 3 in both groups may be attributed to regression of hepatic fibrosis induced by antiviral therapy.[40] A previous study reported that the increase in cumulative HCC incidence decelerated after 5 years of ETV or TDF treatment, compared to the first 5 years.[41] Furthermore, another Korean study using the NHIS database observed a similar trend of HCC incidence among ETV- or TDF-treated patients, supporting the validity of our current results.[7]

It is notable that the absolute incidence of EHM increased in the ETV group but decreased in the TDF group after year 3. Although one may assume that this trend indicates the protumor effects of ETV, it should be interpreted with caution. Preclinical animal studies raised concerns about the potential carcinogenicity of ETV.[16] Although two real-world retrospective studies showed that ETV at usual clinical doses does not increase cancer risk,[17,18] the number of patients analyzed may have been insufficient to avoid a false-negative result, considering the low incidence of EHM. In addition, the protumor effects of ETV were possibly masked by the overall antitumor effects for both IHM and EHM.[19,41] ETV can incorporate into the human genome,[42,43] which may lead to carcinogenicity during subsequent replication cycles. It is possible to assume that the protumor effects of ETV became apparent after cumulative damage caused by ETV exceeded a certain threshold level (approximately 430 mg of ETV in this study). However, the doses of ETV at which its carcinogenic effects were confirmed in the animal experiments, were far higher compared to the approved dose for humans. In addition, since CHB itself increases the risk of both IHM and EHM, the true protumor effects of ETV can only be proven by comparing ETV versus no ETV over a long period time in healthy non-CHB subjects, which is unfeasible.

ETV appears to have potent antitumor effects, considering the decreasing incidence of IHM confirmed in previous studies.[44,45] Therefore, in conjunction with prior evidence suggesting that both ETV and TDF treatments are beneficial in CHB patients for reducing EHM,[19] as well as IHM,[41,44,45] our findings can be interpreted as follows: (i) the antitumor effects of TDF are greater than those of ETV; and (ii) even if ETV has protumor effects in humans, which cannot be proven with certainty in the current setting, these effects are unlikely to be strong enough to overpower its antitumor effects associated with suppressing HBV replication. However, it may be advised that clinicians should be more suspicious of the potential protumor effects of ETV.

This study had several limitations. First, NHIS database

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does not provide detailed individual laboratory data including serum HBV DNA levels. Instead, additional data on anthropometric measurements, health-related behaviors, and blood test results were collected in more than half of the entire cohort who received medical check-up provided by NHIS and same results were maintained. Second, statistical significance was not achieved for the incidence of most individual EHMs, except stomach cancer, breast cancer, and non-Hodgkin lymphoma. Despite the use of a large nationwide cohort, the low incidence of each cancer made it difficult to achieve statistical significance. However, a similar trend of higher risk with ETV was seen for most of the EHMs. Regarding the differences in breast cancer before versus after year 3, a high level of estradiol may have contributed to these results; this requires additional research (see Supplementary Discussion). Third, while an association between the use of ETV or TDF and the incidence of EHM or IHM was assessed, not all aspects of the antivirals, including adverse events, were evaluated. TDF is known to have a higher risk of renal and bone toxicity compared to ETV.[46] Although long-term use of TDF may reduce the risk of EHM, the superiority of TDF cannot be generalized to all patients, as the risks of TDF use may outweigh the benefits in patients with impaired renal function.[47] Fourth, drug modifications or discontinuations during follow-up were not considered. We excluded patients who switched regimens within 90 days of the index date. However, cases in which ETV or TDF was subsequently discontinued or switched were not excluded. Although the number of cases that switched regimens is relatively small, and changes occur in both directions, it may have affected the results of this study as another confounder. Fifth, the results of this study may have limited generalizability, as most CHB patients in South Korea are infected with genotype C HBV.[48] Although comparable overall virologic responses to NAs have been observed among patients with diverse HBV genotypes,[49] further international investigations are required. Lastly, this is a retrospective study, which by its nature cannot show causality, only association. In addition, despite the use of multiple statistical strategies, it is still possible that the results were affected by unmeasured confounders as each cancer has different risk factors. Considering the low incidence of EHMs in patients with CHB, a large randomized controlled trial or prospective study with long-term follow-up is not feasible, and the results of this study need to be validated at least in an independent retrospective cohort.

In conclusion, TDF was associated with approximately 30% reduced risks of both EHM and IHM than ETV after 3 years of treatment. Although the results of this study need to be validated in an independent cohort, the antitumor effects of TDF appeared to be greater than those of ETV.

Authors' contribution

Conceptualization: Moon Haeng Hur, Dong Hyeon Lee, Jeong-Hoon Lee, Sang Hyub Lee, Yong Jin Jung, Yoon Jun Kim, and Jung-Hwan Yoon; Data Curation: Moon Haeng Hur, Dong Hyeon Lee, Jeong-Hoon Lee, Mi-Sook Kim, Jeayeon Park, Hyunjae Shin, Sung Won Chung, and Hee Jin Cho; Formal analysis: Moon Haeng Hur, Dong Hyeon Lee, Jeong-Hoon Lee, Mi-Sook Kim, Min Kyung Park, Heejoon Jang, Yun Bin Lee, and Su Jong Yu; Methodology: Moon Haeng Hur, Dong Hyeon Lee, Jeong-Hoon Lee, Mi-Sook Kim, Jeayeon Park, Hyunjae Shin, Sung Won Chung, and Hee Jin Cho; Supervision: Jeong-Hoon Lee, Sang Hyub Lee, Yong Jin Jung, Yoon Jun Kim, and Jung-Hwan Yoon; Writing - Original Draft: Moon Haeng Hur, Dong Hyeon Lee, and Jeong-Hoon Lee; Writing - Review & Editing: Mi-Sook Kim, Jeayeon Park, Hyunjae Shin, Sung Won Chung, Hee Jin Cho, Min Kyung Park, Heejoon Jang, Yun Bin Lee, Su Jong Yu, Sang Hyub Lee, Yong Jin Jung, Yoon Jun Kim, and Jung-Hwan Yoon.

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Conflicts of Interest

Moon Haeng Hur: Nothing to declare; Dong Hyeon Lee: Nothing to declare; Jeong-Hoon Lee: Receives research grants from Yuhan Pharmaceuticals and GreenCross Cell, lecture fees from GreenCross Cell, Daewoong Pharmaceuticals, and Gilead Korea; Mi-Sook Kim: Nothing to declare; Jeayeon Park: Nothing to declare; Hyunjae Shin: Nothing to declare; Sung Won Chung: Nothing to declare; to declare; Heejoon Jang: Nothing to declare; Yun Bin

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SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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