

## Effects of Entecavir and Tenofovir on Renal Function in Patients with Hepatitis B Virus-Related Compensated and Decompensated Cirrhosis

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**Background/Aims:** The renal effects of nucleos(t)ide analogs in patients with chronic hepatitis B are controversial. We aimed to compare the impact of entecavir (ETV) and tenofovir (TDF) on renal function in patients with hepatitis B virus (HBV)-related cirrhosis. **Methods:** We performed a retrospective cohort study of 235 consecutive treatment-naïve patients with HBV-related cirrhosis who were treated with ETV or TDF between December 2012 and November 2013 at Severance Hospital, Seoul, Korea. **Results:** Compensated cirrhosis was noted in 183 patients (ETV 130, TDF 53), and decompensated cirrhosis was noted in 52 patients (ETV 32, TDF 20). There were no significant changes in estimated glomerular filtration rates (eGFR) from baseline in either the ETV- or TDF-treated groups at week 96 (Chronic Kidney Disease Epidemiology Collaboration, ETV  $-1.68\%$  and TDF  $-5.03\%$ ,  $p=0.358$ ). Using a multivariate analysis, the significant factors associated with a decrease in eGFR  $>20\%$  were baseline eGFR, diabetes mellitus (DM), and the use of diuretics. The use of antiviral agents and baseline decompensation were not determined to be significant factors. **Conclusions:** In patients with HBV-related cirrhosis, TDF has shown similar renal safety to that of ETV over a 2-year period. Renal function should be closely monitored, especially in patients who exhibit decreasing eGFR, DM, and the use of diuretics. (*Gut Liver* 2017;11:828-834)

**Key Words:** Hepatitis B; Fibrosis; Entecavir; Tenofovir; Renal safety

### INTRODUCTION

Renal failure is a challenging complication of cirrhosis. Patients with cirrhosis and renal failure are at high risk for death while awaiting transplantation and have an increased frequency of complications.<sup>1,2</sup> The model for end-stage liver disease score derived from measurements of serum bilirubin, the international normalized ratio of prothrombin time, and serum creatinine (SCr) was introduced as an aid to organ allocation among candidates for liver transplantation.<sup>1</sup> Maintaining renal function is critical for ensuring a positive prognosis in cirrhosis patients.

Chronic hepatitis B (CHB) viral infections are known to have adverse effects on kidney function. Rarely, CHB viral infections can cause deposition of immune complexes, leading to secondary glomerulopathies.<sup>3</sup> Also, various factors such as old age, diabetes mellitus (DM), metabolic syndrome, high blood pressure, human immunodeficiency virus (HIV) or hepatitis C virus coinfection, nephrotoxic drugs, end-stage liver disease, and solid organ transplantation are related to a decrease in kidney function. In addition to infection with hepatitis B virus (HBV), there are many factors associated with decreased renal function in CHB patients. In order to improve treatment of these patients, we must better understand these contributing factors.

Treatments for HBV infection include nucleoside analogues such as lamivudine, telbivudine, and entecavir (ETV), or nucleotide analogues including adefovir dipivoxil (ADV) and tenofovir disoproxil fumarate (TDF). TDF and ETV have been recommended as first line nucleos(t)ide analogues (NUCs) for their antiviral effects, reduced drug resistance, and fewer side effects.<sup>4-6</sup>

NUCs are excreted through the kidney and are known to contribute to a risk of renal impairment attributable to alterations in renal tubular transporters, apoptosis, and mitochondrial toxicity.<sup>7,8</sup> NUC-associated nephrotoxicity is dose-dependent;

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Received on September 30, 2016. Revised on December 17, 2016. Accepted on January 18, 2017. Published online June 27, 2017

pISSN 1976-2283 eISSN 2005-1212 <https://doi.org/10.5009/gnl16484>

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therefore, the dose of antiviral agents is adjusted when used in patients with impaired renal function (creatinine clearance <50 mL/min).<sup>9</sup>

Renal tubular dysfunction develops in 15% of patients treated with ADV or TDF for 2 to 9 years and is partially reversible when the antiviral agent is changed.<sup>10</sup> Currently, there are no definite conclusions regarding nephrotoxicity associated with long-term use of ETV and TDF. ETV and TDF treatments are well tolerated in patients with decompensated liver disease.<sup>11</sup> However, there are case reports of TDF-associated Fanconi syndrome and nephrotic syndrome.<sup>12</sup> Consequently, there is some controversy surrounding the renal effects of NUCs in patients with CHB, especially compensated and decompensated HBV-related cirrhosis. Clinical trials have reported a relatively good renal safety profile for these drugs; however, there are a few reports of tubular damage leading to renal insufficiency after the use of TDF.<sup>13-15</sup>

In this study, we aimed to analyze changes in renal function in patients with compensated and decompensated cirrhosis treated with ETV or TDF for 96 weeks, and to compare the effects of ETV and TDF on renal function in HBV-related cirrhosis patients.

## MATERIALS AND METHODS

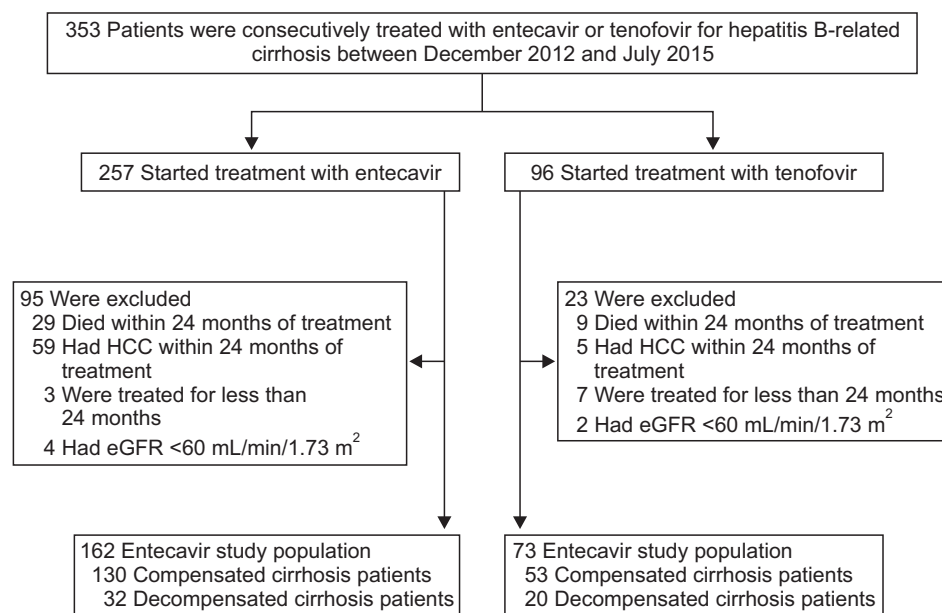
### 1. Patients and study design

We performed a retrospective cohort study of 235 consecutive treatment-naïve patients with HBV-related cirrhosis who were treated with ETV or TDF between December 2012 and November 2013 at Severance Hospital, Seoul, Korea (162 CHB patients who were treated with ETV monotherapy and 73 CHB patients who were treated with TDF monotherapy). Initially, we identified 353 patients who had been administered ETV (72.8%) or

TDF (27.2%) for HBV-related cirrhosis: age  $\geq 18$  years, hepatitis B surface antigen carrier for  $\geq 6$  months; pathologic or clinical evidence of cirrhosis, including nodularity/splenomegaly on liver imaging and/or thrombocytopenia; presentation with the first episode of liver decompensation defined as the occurrence of complications, such as ascites, variceal bleeding, encephalopathy, or spontaneous bacterial peritonitis.<sup>16</sup> Study exclusion criteria included patients with a history of hepatocellular carcinoma within 24 months of treatment, patients that died within 24 months of treatment, patients treated for less than 24 months, patients with massive bleeding events, and patients with baseline estimated glomerular filtration rates (eGFR) below 60 mL/min (Fig. 1). These criteria were considered to be confounding factors that would interfere with an objective analysis of any associations observed between the treatment and renal function. The general treatment of patients followed the guidelines of the Korean Association for the Study of the Liver.<sup>17</sup>

Patients were identified using the Severance Hospital Liver Disease Cohort Registry (SOLID CORE), which is an internal web-based electronic medical record that encompasses CHB patients treated with antiviral therapy at Severance Hospital, Yonsei University College of Medicine. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Severance Hospital.

For each patient, medical records were reviewed to obtain demographic information, baseline CHB characteristics, and comorbidities including hypertension, DM, history of hepatocellular carcinoma, history of organ transplantation, use of diuretics, use of nonsteroidal anti-inflammatory drugs (NSAID) and pre-existing renal insufficiency. Other risk factors for renal disease, including massive bleeding events and concomitant medications were also recorded.



**Fig. 1.** Recruitment algorithm. A total of 353 consecutive patients treated with entecavir or tenofovir for hepatitis B-related cirrhosis were included. Among them, patients with a history of hepatocellular carcinoma (HCC) within 24 months of treatment, patients who died within 24 months of treatment, patients treated for less than 24 months, patients with massive bleeding events, and patients with baseline estimated glomerular filtration rates (eGFR) of less than 60 mL/min were excluded based on our exclusion criteria. A total of 235 patients were selected for the final statistical analysis.

## 2. Renal classifications

Renal function was monitored every 3 to 6 months for every patient. Renal insufficiency was defined as an eGFR of less than 60 mL/min as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>18</sup> Nephrotoxicity associated with TDF and ETV treatments was assessed by measures of renal function such as increased SCr and changes in eGFR. Specific changes in SCr were assessed by review of the medical records after initiation of TDF or ETV therapy; the data were used in the CKD-EPI equation for calculating renal function to determine eGFR. All available SCr assessments from the medical records were used in the data analysis.

## 3. Statistical analysis

Means and standard deviations were calculated for all continuous variables. Categorical variables were expressed as proportions (%) and analyses were used to compare groups of these variables. Independent sample t-tests were performed to compare means between groups for continuous variables. Multivariate logistic regression analyses were carried out on the combined treatment groups to identify the evaluate predictors for variables including age, sex, DM, hypertension, use of diuretics, use of NSAID, pre-existing renal insufficiency, compensated

or decompensated cirrhosis, and antiviral agents. All statistical analyses were assessed using the SPSS version 20.0 (IBM Corp., Armonk, NY, USA). A p-value less than 0.05 was considered statistically significant.

## RESULTS

### 1. Characteristics of the patients and data collection

Data were collected from January 1, 2012 to August 1, 2015. Baseline characteristics are summarized in Table 1. Prior to treatment initiation, mean age was 55.8±8.5 years, and 66.0% of the study participants were male. All patients were Asian. Similar percentages of both treatment groups had DM (ETV 21.6% and TDF 19.2%) and hypertension (ETV 24.7% and TDF 20.5%). Baseline HBV DNA levels were slightly higher in the ETV treatment group than the TDF treatment group (log 5.6 IU/mL and log 5.4 IU/mL, p=0.125). Baseline creatinine levels (ETV 0.9 mg/dL and TDF 0.8 mg/dL, p=0.209) and eGFR (CKD-EPI equation, ETV 92.7 mL/min/1.73 m<sup>2</sup> and TDF 98.2 mL/min/1.73 m<sup>2</sup>, p=0.272) were similar in both treatment groups. There were no significant differences in baseline alanine aminotransferase, aspartate aminotransferase, calcium, phosphate, and blood urea nitrogen levels, use of diuretics, and use of NSAID.

**Table 1.** Baseline Characteristics

Variable	Total (n=235)	ETV group (n=162)	TDF group (n=73)	p-value*
Demographic data				
Age, yr	55.8±8.5	55.6±8.4	56.4±8.5	0.946
Male sex	155 (66.0)	110 (68.0)	45 (61.6)	0.088
Diabetes mellitus	49 (20.9)	35 (21.6)	14 (19.2)	0.498
Hypertension	55 (23.4)	40 (24.7)	15 (20.5)	0.220
Decompensated LC/compensated LC	52 (22.1)/183 (77.9)	32 (19.8)/130 (80.2)	20 (27.3)/53 (72.7)	0.014
NSAID medication	27 (11.5)	18 (11.1)	9 (12.3)	0.738
Diuretics medication	17 (7.2)	13 (8.0)	4 (5.5)	0.515
Laboratory data				
HBV DNA log <sub>10</sub> IU/mL	5.4±1.5	5.6±1.6	5.4±1.3	0.125
HBeAg positive/negative	101 (42.3)/138 (57.7)	73 (44.0)/93 (56.0)	28 (38.3)/45 (61.7)	0.091
AST, IU/L	107.8±362.2	114.7±420.0	92.5±177.6	0.699
ALT, IU/L	106.1±271.9	109.3±300.9	99.0±194.1	0.800
Calcium, mg/dL	8.7±0.5	8.7±0.5	8.7±0.5	0.180
Phosphate, mg/dL	3.5±2.1	3.6±2.5	3.3±0.5	0.292
Blood urea nitrogen, mg/dL	13.6±4.1	13.6±4.1	13.6±4.3	0.829
Creatinine, mg/dL	0.8±0.2	0.9±0.2	0.8±0.2	0.209
eGFR (CKD-EPI), mL/min/1.73 m <sup>2</sup>	94.42±12.673	92.7±12.8	98.2±11.68	0.272

Data are presented as mean±SD or number (%).

ETV, entecavir; TDF, tenofovir; LC, liver cirrhosis; NSAID, nonsteroidal anti-inflammatory drug; HBV, hepatitis B virus; HBeAg, hepatitis B envelope antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

\*p-values for comparing the ETV and TDF groups.

## 2. Changes in renal markers

We analyzed renal function change over time in ETV-treated and TDF-treated patients. However, there were no significant changes in eGFR from baseline in either the ETV- or TDF-treated groups at weeks 96 (CKD-EPI, ETV -1.68% and TDF -5.03%,  $p=0.358$ ) (Table 2); changes in SCr from baseline in both ETV- and TDF-treated groups were also statistically insignificant (ETV

2.54% and TDF 9.09%,  $p=0.396$ ). Also, subanalysis of patients with compensated cirrhosis and decompensated cirrhosis were demonstrated in renal function change. The mean eGFR was 0.72% lower in the ETV-treated group with compensated cirrhosis at week 96 than at baseline, and the mean eGFR was 5.37% lower in the TDF-treated group after treatment than at baseline ( $p=0.220$ ). The mean eGFR was 5.57% lower in the ETV-treated group with decompensated cirrhosis after treatment than at

**Table 2.** Changes in Renal Markers

Marker	Group (n)	Baseline	Week 48	Week 96	LS mean±SE change (%) from baseline to week 96	p-value*
eGFR (CKD-EPI), mL/min/1.73 m <sup>2</sup>						
All patients	ETV group (162)	92.73±12.77	89.50±15.79	90.69±16.53	-1.68	0.358
	TDF group (73)	98.18±11.68	95.77±11.75	93.11±13.71	-5.03	
Compensated cirrhosis patients	ETV group (130)	92.03±13.06	89.16±14.75	90.77±15.50	-0.72	0.220
	TDF group (53)	97.96±11.78	94.42±11.39	92.64±13.62	-5.37	
Decompensated cirrhosis patients	ETV group (32)	95.56±11.29	90.88±19.69	90.34±19.50	-5.57	0.778
	TDF group (20)	98.75±11.70	99.35±12.22	94.35±14.21	-4.13	
Creatinine, mg/dL						
All patients	ETV group (162)	0.87±0.16	0.90±0.26	0.91±0.22	2.54	0.396
	TDF group (73)	0.76±0.17	0.79±0.16	0.82±0.16	9.09	
Compensated cirrhosis patients	ETV group (130)	0.89±0.16	0.91±0.20	0.89±0.20	1.27	0.285
	TDF group (53)	0.76±0.17	0.80±0.15	0.82±0.18	9.11	
Decompensated cirrhosis patients	ETV group (32)	0.81±0.13	0.87±0.30	0.98±0.09	7.72	0.881
	TDF group (20)	0.78±0.19	0.78±0.18	0.83±0.04	9.05	
Calcium, mg/dL						
All patients	ETV group (162)	8.66±0.55	8.84±0.53	8.94±0.61	3.46	0.218
	TDF group (73)	8.74±0.55	8.81±0.54	8.89±0.46	2.06	
Phosphate, mg/dL						
All patients	ETV group (162)	3.63±2.46	3.83±4.66	3.39±0.56	1.69	0.548
	TDF group (73)	3.34±0.58	3.36±0.56	3.34±0.53	3.20	

LS, least square; SE, standard error; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ETV, entecavir; TDF, tenofovir.

\*p-values for comparing the ETV and TDF groups.

**Table 3.** Changes in Renal Markers Following Treatment

	TDF	ETV	p-value*
All patients (n=235)	n=73	n=162	
SCr increase >0.2 mg/dL	6 (8.2)	16 (9.9)	0.686
eGFR<60 mL/min (CKD-EPI)	2 (2.7)	6 (3.7)	0.524
Decrease in eGFR >20% (CKD-EPI)	5 (6.8)	13 (8.0)	0.754
Decompenstated cirrhosis patients (n=52)	n=20	n=32	
SCr increase >0.2 mg/dL	2 (10.0)	6 (18.8)	0.463
eGFR<60 mL/min (CKD-EPI)	0	2 (6.3)	0.374
Decrease in eGFR >20% (CKD-EPI)	2 (10.0)	5 (15.6)	0.563

TDF, tenofovir; ETV, entecavir; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

\*p-values for comparing the ETV and TDF groups.

baseline, and the mean eGFR was 4.13% lower in the TDF-treated group after treatment than at baseline ( $p=0.778$ ); however, these results were statistically insignificant.

During treatment, increases in SCr  $>0.2$  mg/dL over baseline values occurred in 9.9% of ETV-treated patients and 8.2% of TDF-treated patients ( $p=0.686$ ) (Table 3); we found no significant differences in renal function between the treatment groups using this direct measure of nephrotoxicity. Using the CKD-EPI equation, we calculated a  $>20\%$  decrease in eGFR from baseline in 13 (8.0%) and five (6.8%) patients in the ETV-treatment and TDF-treatment groups, respectively ( $p=0.754$ ). Six (3.7%) patients in the ETV-treatment group and two (2.7%) patients in the TDF-treatment group developed an eGFR below 60 mL/min/1.73 m<sup>2</sup> during therapy ( $p=0.524$ ), which differed from their baseline values.

### 3. Changes in eGFR in patients with renal insufficiency

A sub-analysis of patients with baseline CKD stage 2 (60 to 89 mL/min/1.73 m<sup>2</sup>) showed that three (4.1%) patients in the TDF-treated group had improvements in eGFR ( $\geq 90$  mL/min/1.73 m<sup>2</sup>) after 96 weeks of treatment (Table 4). In comparison, 21 (13.0%) patients in the ETV-treated group had improvements in eGFR ( $\geq 90$  mL/min/1.73 m<sup>2</sup>) after 96 weeks of treatment. A subanalysis of patients with baseline CKD stage showed that 16 (21.9%) of the TDF-treated group had impaired renal function after treatment than at baseline, whereas 31 (19.1%) of the ETV-treated group had impaired renal function after treatment than at baseline.

**Table 4.** Changes in eGFR Category (CKD-EPI Equation)

	Patients in eGFR categories at end of study			Total
	<60	60–90	>90	
<b>Tenofovir group</b>				
Patients in eGFR categories at baseline				
60–90	2 (2.7)	11 (15.1)	3 (4.1)	16 (21.9)
>90	0	14 (19.2)	43 (58.9)	57 (78.1)
Total	2 (2.7)	25 (34.2)	46 (63.0)	73 (100)
Impaired renal function	16 (21.9)			
<b>Entecavir group</b>				
Patients in eGFR categories at baseline				
60–90	4 (2.5)	37 (22.8)	21 (13.0)	62 (38.3)
>90	2 (1.2)	25 (15.4)	73 (45.1)	100 (61.7)
Total	6 (3.7)	62 (38.3)	94 (58.0)	162 (100)
Impaired renal function	31 (19.1)			

Data are presented as number (%).

eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

**Table 5.** Independent Risk Factor for Decreases in eGFR  $>20\%$  (CKD-EPI Equation)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Tenofovir (vs entecavir)	1.195 (0.410–3.485)	0.745	1.393 (0.434–4.472)	0.578
Male sex	1.355 (0.465–3.946)	0.578		
Age	0.977 (0.924–1.034)	0.426		
History of hypertension	2.957 (1.104–7.918)	0.003	2.378 (0.769–7.356)	0.133
History of diabetes mellitus	5.855 (2.168–15.813)	0.001	5.692 (1.823–17.776)	0.003
Use of diuretics	8.104 (2.612–25.147)	0.001	20.170 (5.043–80.672)	<0.001
Use of NSAID	2.985 (0.990–9.002)	0.052		
eGFR (CKD-EPI)	1.060 (1.014–1.108)	0.009	1.043 (1.002–1.084)	0.038
Compensated cirrhosis (vs decompensated cirrhosis)	2.418 (0.887–6.592)	0.084		

eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HR, hazard ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.



#### 4. Independent risk factors for a decline in eGFR >20% (CKD-EPI equation)

Univariate analysis and multivariate analysis of factors associated with markers of renal impairment were carried out on the combined treatment groups for all patients (n=235). By multivariate analysis, significant factors associated with a decrease in eGFR >20% included baseline eGFR (adjusted odds ratio [OR], 1.043; 95% confidence interval [CI], 1.002 to 1.084; p=0.038), DM (OR, 5.692; 95% CI, 1.823 to 17.776; p=0.003), and use of diuretics (OR, 20.170; 95% CI, 5.043 to 80.671; p<0.001) (Table 5). Exposure to TDF was not a significant predictor.

## DISCUSSION

About one-third of the population worldwide has been infected with HBV at some point, and 350 to 400 million people are chronic HBV surface antigen carriers.<sup>17</sup> In many of these patients, HBV infection proceeds to cirrhosis and eventually end-stage liver disease, hepatocellular carcinoma, and death. Antiviral therapy in HBV-related compensated and decompensated cirrhosis patients helps regress fibrosis and reverse cirrhosis.<sup>16,19</sup> In these patients, ETV and TDF are preferred for their potency and minimal resistance.<sup>17,20,21</sup>

ETV and TDF are preferred in CHB patients for their less adverse effects compared to other antiviral agents. There are few reports of TDF-associated nephrotoxicity in HIV-positive and CHB patients. However, real life observations studies of CHB patients state that using TDF does not significantly reduce renal function compared to ETV.<sup>22-24</sup> The studies analyzed eGFR decrease magnitude and concluded cumulative incidences of patients with decreased eGFR >20% did not differ between ETV and TDF cohorts.<sup>25,26</sup> However, there are limited data in cirrhosis patients, who have potential renal dysfunction.

This study evaluated renal function changes in HBV-related compensated and decompensated cirrhosis patients who received ETV or TDF treatment for 2 years. To our knowledge, this is the first study to examine renal impairment of ETV and TDF in cirrhosis patients. The mean eGFR was 5.02% lower in the decompensated group at week 96 than at baseline, and the mean eGFR was 2.07% lower in the compensated group after treatment than at baseline (p=0.397). These data suggest that ETV and TDF have similar renal safety profiles.

The Cockcroft-Gault equation, modification of diet in renal disease (MDRD) equation, and CKD-EPI equation are commonly used to calculate eGFR. Recent studies have shown that the CKD-EPI equation is more accurate than the MDRD equation for estimating eGFR.<sup>14</sup> Thus, in this study we calculated eGFR using the CKD-EPI equation to evaluate renal function in ETV- and TDF-treated patients. In patients with an increase in SCr of 0.2 mg/dL or greater, we additionally analyzed the proportion of patients with CKD stage grade 3 or higher and impaired eGFR

(CKD-EPI) >20% of baseline for each group. There were no statistically significant differences observed.

Since many patients included in this study had multiple medical histories and comorbidities, we proceeded with multivariate analysis to determine variables related to impaired renal function. DM, low baseline eGFR, and the use of diuretics were determined to be independent risk factors for impaired renal function, consistent with previous studies.<sup>27</sup> Although DM is a risk factor for impaired renal function in ETV- and TDF-treated patients, it is difficult to delineate whether the renal impairment is attributable to treatment with antiviral agents or DM-associated nephropathy. Extreme caution is required when using ETV and TDF in patients with comorbidities. In addition to DM, low baseline eGFR as an independent risk factor, reflects the importance of dose adjustment when administering ETV and TDF. Multivariate analysis revealed that use of ETV or TDF is not an independent risk factor for impaired renal function (OR, 1.393; 95% CI, 0.434 to 4.472; p=0.578).

The data used for these analyses were gathered from several physicians instead of one, which is a limitation of this study. Also, the study design, based on short-term retrospective chart reviews, is a limitation. Short duration of TDF use in our patients is our limitation, and long term study is required in the future. The data were collected precisely every 3 months for each patient, which is a strength of this study. Larger prospective future studies may accurately determine differences in safety between TDF and ETV.

In conclusion, in patients with HBV-related compensated or decompensated cirrhosis, there was no significant difference concerning impaired renal function between ETV and TDF for 2 years. With treatment-related renal safety concern, regular renal function should be monitored, especially high-risk patients such as those with baseline low eGFR, DM, and receiving concomitant nephrotoxic drugs.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGEMENTS

This study was supported by a fund of the HBV cohort study (4800-4845-300-260, 2016-ER5103-00) from the Korea Centers for Disease Control and Prevention.

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