의학석사 학위논문

항바이러스제 치료 중인 만성 B 형 간염 환자의 신기능의 종단적 변화

Longitudinal Changes in Renal Function in Patients with Chronic Hepatitis B on Antiviral Treatment

울산대학교 대학원

의 학 과

조 민 주

항바이러스제 치료 중인 만성 B 형 간염 환자의 신기능의 종단적 변화

지 도 교 수 임 영 석

이 논문을 의학석사 학위 논문으로 제출함

2024 년 2 월

울산대학교 대학원

의 학 과

조 민 주

조민주의 의학석사 학위 논문을 인준함

심사위원　　최 종 기　　인

심사위원　　백 충 희　　인

심사위원　　임 영 석　　인

울 산 대 학 교　대 학 원

2024 년 2 월

국문요약

연구배경: 뉴클레오시(티)드 유사체(Nucleos(t)ide, NUC)를 복용하는 만성 B 형 간염 환자는 종종 신기능 저하를 경험한다. 최근 NUC 복용이 신기능에 미치는 영향에 대해 상충된 결과가 보고되었다. 이에 본 연구는 치료하지 않는 만성 B 형 간염 환자와 NUC 종류에 따른 신기능의 종단적 변화를 알아보고자 하였다.

연구방법: 2014 년부터 2022 년까지 만성 B 형 간염 환자 10,642 명을 후향적으로 분석하였다. 일차 결과는 만성 신질환의 진행으로, 최소 한 단계 이상의 신기능 악화로 정의하였다. 성향점수 매칭(Propensity score matching) 방법을 사용하여 비치료군과 NUC 종류에 따른 치료군을 각각 비교하였다.

연구결과: 1,966 쌍의 성향점수(PS) 일치 코호트에서 NUC 치료군(7.6/100 인년)의 만성 신질환 진행 위험 비율은 비치료군(4.4/100 인년)보다 유의하게 높았으며, 위험비(hazard ratio)는 1.70 이었다($p<0.001$). 테노포비르 디소프록실 푸마르산염(TDF) 치료군(7.9/100 인년)은 PS 일치된 비치료군(4.5/100 인년)과 비교하여 1.76 배 높은 만성 신질환 진행 위험을 보였다($p<0.001$). 엔테카비르(ETV)와 테노포비르 알라페나미드(TAF) 치료군은 PS 일치 코호트 755 쌍과 426 쌍에서 모두 비치료군과 비슷한 만성 신질환 진행 위험을 보였다(각각 $p=0.132$ 와 $p=0.120$). 엔테카비르(ETV) 치료군(6.0/100 인년)과 테노포비르 알라페나미드(TAF) 치료군(5.2/100 인년)을 비교한 PS 일치 코호트 510 쌍에서는 유의미한 만성 신질환 진행 위험 차이는 확인되지 않았다($p=0.118$).

연구결론: NUC 치료군, 특히 테노포비르 디소프록실 푸마르산염(TDF) 치료군이 비치료군보다 만성 신질환 진행 위험이 유의미하게 높았다. 엔테카비르(ETV) 및 테노포비르 알라페나미드(TAF) 치료군은 비치료군과 비슷한 만성 신질환 진행 위험을 보였다. 엔테카비르(ETV)와 테노포비르 알라페나미드(TAF) 치료군 사이에는 유의미한 차이가 관찰되지 않았다.

Contents

List of tables and figures

Introduction

Oral nucleos(t)ide analogues (NUCs) have been shown to reduce the development of hepatocellular carcinoma (HCC) and prevent liver disease progression by suppressing hepatitis B virus (HBV) replication in patients with chronic hepatitis B (CHB).(1) Current international guidelines for CHB recommend entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) as the preferred NUCs.(2-4) However, despite these therapies, hepatitis B surface antigen (HBsAg) clearance occurs very rarely, necessitating lifelong NUC treatment. As patients with CHB live longer than before, a decline in renal function due to aging is expected, and the prevalence of comorbidities such as diabetes, hypertension, and chronic kidney disease (CKD) has increased.(5) Furthermore, patients with CHB have a higher prevalence of CKD than the general population.(6, 7) In light of this, preserving renal function in patients with CHB receiving long-term NUCs is a major concern.

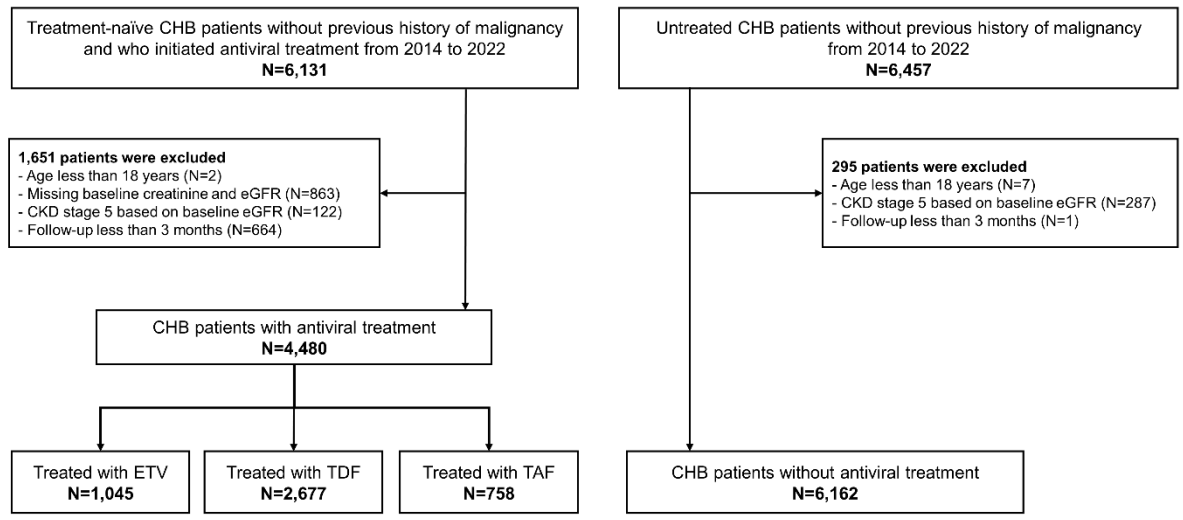
Previous studies have reported that patients on NUCs experienced a steeper reduction in renal function than expected, especially in those receiving TDF compared with ETV.(8-11) Another study found no significant difference in the decline in renal function between patients on ETV and those who were untreated.(9) TAF, the most recently approved therapy, is known to be associated with less nephrotoxicity than TDF. Interestingly, recent studies have indicated that patients on ETV have a higher risk of renal function decline than those on TAF and untreated patients.(12, 13) However, these studies were limited by the small number of included patients and relatively short follow-up periods. Therefore, we aimed to comprehensively examine the longitudinal changes in renal function in patients with CHB and to compare the decline in renal function based on treatment status and type in a large real-world cohort.

Methods

Study design and subject

This was a historical cohort study of patients with CHB treated from 2014 to 2022 at Asan Medical Center, a 2,700-bed academic tertiary referral center, in Seoul, Republic of Korea. Patients meeting all the following criteria were included in the study: (1) HBsAg positivity for more than six months; (2) no history of HCC or non-HCC malignancy; and (3) no history of NUC treatment. Patients meeting any of the following criteria were excluded; (1) age younger than 18 years; (2) missing information for the estimated glomerular filtration rate (eGFR); (3) CKD stage 5 at baseline; (4) follow-up period less than three months; or (5) coinfection with hepatitis C virus, hepatitis D virus, human immunodeficiency virus (HIV), or other hepatotropic viruses. Based on the use of NUCs, patients were divided into the treated group and the untreated group. Patients in the treated group received either ETV (0.5 mg/day), TDF (300 mg/day), or TAF (25 mg/day). Notably, TAF was only approved in Korea in September 2017. Hence, prior to its approval, ETV and TDF were the primary treatment options chosen for our study population. The untreated patients had not received any NUC treatment during the study period. Our study ultimately included 4,480 treated patients and 6,162 untreated patients (Figure 1).

This study received approval from the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (IRB number: 2020-0315). Due to the retrospective nature of the evaluation, informed consent from the IRB could not be obtained. All procedures and reporting adhered to the guidelines of observational studies in epidemiology.



CHB: Chronic hepatitis B, CKD: chronic kidney disease, HCC: hepatocellular carcinoma, eGFR: estimated glomerular filtration rate, ETV: entecavir, TAF: tenofovir alafenamide, TDF: tenofovir disoproxil fumarate

Figure 1. Study flow of the screening and selection of the study population

Clinical and laboratory variables

Data for this study were obtained from electronic medical records at Asan Medical Center. The baseline demographic variables of the enrolled study subjects included age, sex, height, weight, and body mass index (BMI). Information about comorbidities including diabetes and hypertension was also collected. Laboratory tests comprised alanine aminotransferase (ALT), albumin, total cholesterol, total bilirubin, creatinine, platelet, prothrombin time, and eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.(14) HBV-related variables included HBeAg and HBV DNA levels. Liver cirrhosis was defined as a shrunken liver volume, the presence of a nodular liver surface and splenomegaly on ultrasonography or computed tomography, clinical features of portal hypertension (e.g., ascites, splenomegaly, or varices). All patients had undergone routine clinical examinations, liver function testing, renal function testing, and measurement of HBV-related variables with HCC surveillance at baseline and every 3–6 months during follow-up.

Study outcomes

The primary study outcome of interest was the progression of CKD. This was defined as an elevation in CKD stage by at least one stage for at least three consecutive months during the study period, which is a criterion consistently used in prior studies.(9, 12, 13) The secondary outcomes involved comparing the longitudinal changes in eGFR based on the type of NUC, using the untreated group as a reference. We additionally compared both the incidence of CKD progression and the longitudinal changes in eGFR between patients treated with ETV and TAF, and patients treated with ETV and TDF, respectively.

Statistical analysis

Data are summarized as median and interquartile range for continuous variables and numbers with percentages for categorical variables. The cumulative rate of CKD progression was estimated using the Kaplan-Meier method and compared using the log-rank test. The incidence rate of CKD progression was calculated per 100 person-years (PYs), and 95% confidence intervals (CIs) were estimated using Poisson distribution. We defined baseline as the initiation of NUC treatment in treated group and by the first monitoring visit since 2014 during follow-up in the untreated group. For the primary outcome, the survival period was calculated from the date of NUC initiation to the first date if progression of CKD

stage ≥1 was subsequently performed. The patients were followed up until the earliest of the following events: diagnosis of HCC, death of any cause, liver transplantation, change in treatment regimen, last follow-up date, or March 2023. The median follow-up duration was 3.7 years with 40,002 PYs in the entire study population.

Due to the considerable difference in baseline characteristics among the groups, we applied propensity score (PS) matching to minimize confounders to compare the outcomes between the treated and untreated groups, 1) ETV-treated and untreated groups, 2) TDF-treated and untreated groups, 3) TAF-treated and untreated groups, 4) ETV-treated and TAF-treated groups, and 5) ETV-treated and TDF-treated groups. Multiple imputation using linear interpolation with the *MICE* package was used to estimate missing values, which comprised 1.18% to 3.53% of the baseline laboratory data. PSs for comparing the treated (as well as ETV, TDF, and TAF) and untreated groups were computed using the following 15 variables: age, sex, height, weight, BMI, diabetes, hypertension, liver cirrhosis, platelet, prothrombin time, creatinine, albumin, total cholesterol, eGFR, and follow-up period. ALT, total bilirubin, and HBV DNA levels were not included in the calculation for PSs in comparisons with the untreated group. Patients requiring NUCs inherently had elevated ALT and HBV DNA levels, and sometimes had increased total bilirubin levels, whereas untreated patients had stable levels of these variables as the untreated patients were not indicated to initiation the NUC treatment. However, when comparing the ETV- and TAF-treated groups and when comparing the ETV- and TDF-treated groups, ALT, total bilirubin, and HBV DNA levels were added to calculate the PSs for matching. A 1:1 nearest-neighbor matching scheme with a caliper size of 0.2 was used for PS matching in each comparison. Finally, 1,996 PS-matched pairs were generated to compare the outcomes between the treated and untreated groups. ETV-treated (755 pairs), TDF-treated (1,201 pairs), and TAF-treated (426 pairs) groups were matched to the untreated group by PS matching. In addition, a total of 510 PS-matched pairs were used to compare the outcomes between the ETV-treated and TAF-treated groups, and 996 PS-matched pairs were made between ETV-treated and TDF-treated groups.

All statistical analyses were performed using the R program (http://cran.r-project.org/). All reported P values are 2-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population

The baseline characteristics of the 10,642 included patients are presented in Table 1. The baseline median eGFR was significantly higher in the untreated group (99.0 mL/min/1.73m^2) than in the treated group (90.0 mL/min/1.73m^2 for ETV, TDF, and TAF). The treated group had a higher prevalence of liver cirrhosis, elevated ALT levels, and elevated HBV DNA levels than the untreated group.

Comparison between the treated and untreated groups

The baseline characteristics of the 1,996 PS-matched pairs used to compare the treated and untreated groups are summarized in Table 1. No significant difference in the baseline characteristics was observed between the two groups except in the ALT levels, HBeAg positivity, and HBV DNA levels, which consisted of treatment criteria for CHB. The baseline median eGFRs in the treated and untreated groups were not significantly different at 94.0 mL/min/1.73m^2 and 96.0 mL/min/1.73m^2, respectively.

During the 13,300 PYs of observation, 436 and 331 patients experienced CKD progression in the treated and untreated groups, respectively. The incidence rate (95% CI) per 100 PYs of CKD progression was 7.6 (6.9–8.3) in the treated group and 4.4 (3.9–4.9) in the untreated group (Table 3). Taking the untreated group as the reference group, the treated group showed a significantly increased risk of CKD progression with a hazard ratio (HR) of 1.70 (95% CI: 1.47–1.97; P <0.001, Figure 2A). Over the study period, both the treated and untreated groups showed a decreasing trend in the median change from baseline in eGFR (Table 3). The treated group appeared to have a greater decrease in the median change in eGFR than the untreated group; however, this difference was not statistically significant. However, after two years of observation, the treated group showed a significantly greater decrease in the median change in eGFR (Figure 3A and Table 4).

Table 1. Baseline characteristics of the study population in the entire cohort and propensity score-matched cohort

	Entire cohort				PS-matched cohort		
	Treated (N=4,480)			Untreated (N=6,162)	Treated (N=1,996)	Untreated (N=1,996)	ASD
	ETV (N=1,045)	TDF (N=2,677)	TAF (N=758)				
Demographic characteristics							
Age, years	53.9 [46.3, 59.7]	50.0 [41.1, 56.9]	49.1 [41.6, 57.7]	52.0 [42.7, 59.5]	51.4 [42.0, 59.1]	51.0 [41.5, 59.2]	0.004
Male, n (%)	609 (58.3)	1,576 (58.9)	422 (55.7)	3,270 (53.1)	1,097 (55.0)	1,133 (56.8)	0.036
Height, cm	165 [158, 172]	166 [159, 173]	167 [159, 173]	165 [158, 172]	165 [158, 172]	167 [159, 170]	0.089
Weight, kg	65.8 [57.2, 75.0]	66.0 [57.0, 74.8]	66.6 [57.1, 75.5]	65.5 [56.6, 73.5]	64.9 [56.0, 74.0]	67.0 [58.0, 74.0]	0.093
Body mass index, kg/m^2	24.4 [22.1, 26.6]	23.9 [21.8, 26.2]	24.0 [21.8, 26.4]	23.9 [21.9, 26.0]	23.8 [21.6, 26.1]	23.8 [21.8, 26.0]	0.020
Comorbidities							
Hypertension, n (%)	106 (10.1)	143 (5.3)	30 (4.0)	1,331 (21.6)	213 (10.7)	230 (11.5)	0.027
Diabetes, n (%)	130 (12.4)	232 (8.7)	34 (4.5)	436 (7.1)	132 (6.6)	140 (7.0)	0.016
Liver cirrhosis, n (%)	506 (48.4)	1362 (50.9)	293 (38.7)	852 (13.8)	458 (22.9)	487 (24.4)	0.034
Laboratory findings							
Platelet count, × 10^3/μL	167 [115, 218]	169 [120, 214]	181 [146, 224]	204 [166, 240]	196 [158, 235]	197 [160, 234]	0.044
ALT, IU/L	45 [17, 139]	45 [25, 96]	58 [30, 117]	22 [16, 34]	39 [21, 96]	24 [16, 38]	0.231
Total bilirubin, mg/dl	0.7 [0.5, 1.1]	0.8 [0.6, 1.1]	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.018
Prothrombin time, INR	1.1 [1.0, 1.1]	1.1 [1.0, 1.1]	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	0.041
Albumin, g/dl	3.9 [3.5, 4.2]	3.9 [3.6, 4.2]	3.9 [3.7, 4.1]	4.2 [3.9, 4.4]	4.0 [3.8, 4.3]	4.1 [3.8, 4.3]	0.007
Creatinine, mg/dl	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	0.8 [0.7, 1.0]	0.045
eGFR, ml/min/1.73m^2	90 [81, 96]	90 [87, 101]	90 [87, 101]	99 [90, 107]	94 [88, 107]	96 [85, 105]	0.026
Baseline CKD stage, n (%)							
Stage 1: ≥90 mL/min	635 (60.8)	1919 (71.7)	530 (69.9)	4,749 (77.1)	1,446 (72.4)	1,311 (65.7)	
Stage 2: 60–89 mL/min	306 (29.3)	674 (25.2)	212 (28.0)	1,314 (21.3)	465 (23.3)	627 (31.4)	
Stage 3: 30–59 mL/min	87 (8.3)	74 (2.8)	14 (1.8)	83 (1.3)	58 (2.9)	57 (2.9)	
Stage 4: 15–29 mL/min	17 (1.6)	10 (0.4)	2 (0.3)	16 (0.3)	27 (1.4)	1 (0.1)	
Total cholesterol, mg/dl	175 [147, 199]	168 [144, 192]	183 [161, 208]	182 [158, 205]	177 [154, 201]	178 [155, 202]	0.002
HBV DNA, $\log_{10}$IU/ml	4.0 [2.0, 7.0]	5.3 [2.3, 7.0]	5.7 [4.0, 7.3]	2.7 [1.7, 3.8]	4.3 [1.7, 6.9]	2.9 [1.8, 4.8]	0.272
HBeAg positivity, n (%)	351 (33.6)	1,283 (47.9)	345 (45.5)	763 (17.9)	700 (44.9)	313 (23.4)	0.465

Note: Data are presented as a frequency and proportion or a median value with an interquartile range.
Abbreviations: ASD, absolute standardized difference; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; ALT, alanine aminotransferase; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen.

Table 2. Baseline characteristics of the study population in the propensity score-matched cohort by types of nucleos(t)ide analogues

	ETV (N=755)	Untreated (N-755)	ASD	TDF (N=1,201)	Untreated (N=1,201)	ASD	TAF (N=426)	Untreated (N=426)	ASD
Demographic characteristics									
Age, years	54 [46, 60]	53 [45, 61]	<0.001	51 [41, 59]	50 [41, 58]	0.011	51 [43, 60]	51 [41, 59]	0.052
Male, n (%)	425 (56.3)	426 (56.4)	0.003	680 (56.6)	692 (57.6)	0.020	231 (54.2)	249 (58.5)	0.085
Height, cm	164 [158, 172]	166 [158, 171]	0.040	165 [158, 172]	166 [159, 173]	0.050	165 [159, 172]	167 [163, 175]	0.045
Weight, kg	65 [57, 74]	67 [57, 76]	0.081	65 [56, 74]	66 [58, 75]	0.057	66 [57, 76]	68 [61, 74]	0.025
BMI, kg/m^2	24 [22, 26]	24 [22, 27]	0.033	24 [22, 26]	24 [22, 26]	0.020	24 [22, 26]	23 [22, 24]	0.044
Comorbidities									
Hypertension, n (%)	95 (12.6)	107 (14.2)	0.047	109 (9.1)	135 (11.2)	0.072	28 (6.6)	33 (7.7)	0.046
Diabetes, n (%)	72 (9.5)	79 (10.5)	0.031	85 (7.1)	83 (6.9)	0.007	18 (4.2)	15 (3.5)	0.037
Liver cirrhosis, n (%)	249 (33.0)	235 (33.5)	0.011	350 (29.1)	354 (29.5)	0.007	111 (26.1)	113 (26.5)	0.011
Laboratory findings									
Platelet count, $\times 10^3/\mu L$	186 [144, 233]	192 [155, 229]	0.010	194 [152, 231]	195 [156, 232]	0.040	187 [153, 230]	194 [159, 231]	0.027
ALT, IU/L	45 [23, 123]	22 [16, 37]	0.169	45 [23, 112]	25 [17, 39]	0.266	67 [28, 123]	25 [16, 40]	0.475
Total bilirubin, mg/dl	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.094	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.017	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.076
Prothrombin time, INR	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	0.056	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	0.044	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	0.038
Albumin, g/dl	4.0 [3.7, 4.2]	4.0 [3.7, 4.2]	0.064	4.0 [3.8, 4.3]	4.1 [3.8, 4.3]	0.002	3.9 [3.7, 4.1]	4.0 [3.7, 4.3]	0.046
Creatinine, mg/dl	0.8 [0.7, 0.9]	0.9 [0.8, 1.0]	0.072	0.8 [0.7, 0.9]	0.8 [0.7, 1.0]	0.036	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	0.032
eGFR, $ml/min/1.73m^2$	90 [84, 99]	89 [76, 101]	0.055	96 [88, 108]	96 [85, 106]	0.044	96 [88, 106]	97 [85, 107]	0.021
Total cholesterol, mg/dl	179 [152, 203]	177 [152, 200]	0.072	174 [151, 198]	176 [153, 198]	0.007	183 [161, 208]	183 [157, 208]	0.066
HBV DNA, $log_{10}IU/ml$	4.3 [2.0, 5.4]	2.7 [1.5, 4.6]	0.182	4.8 [1.9, 7.0]	2.9 [1.7, 4.8]	0.371	5.6 [4.0, 7.3]	3.0 [1.8, 5.0]	0.783
HBeAg positivity, n (%)	169 (31.5)	114 (23.6)	0.177	463 (50.6)	186 (23.5)	0.584	172 (45.4)	71 (24.1)	0.459

Note: Data are presented as a frequency and proportion or a median value with an interquartile range.
Abbreviations: ASD, absolute standardized difference; BMI, body mass index; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; ALT, alanine aminotransferase; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen.

Comparison between the ETV-treated and untreated groups

A total of 755 PS-matched pairs were generated to compare the ETV-treated and untreated groups. The baseline characteristics of both PS-matched pairs did not significantly differ, except the ALT levels, HBeAg positivity and HBV DNA levels (Table 2).

The incidence rate of CKD progression in the ETV-treated and untreated groups was 6.8 (95% CI: 5.8–8.0)/100 PYs and 5.6 (95% CI: 4.7–6.5)/100 PYs, respectively, during the 4,889 PYs of observation (Table 3). No significant difference in the risk of CKD progression was observed between the ETV-treated and untreated groups (HR: 1.19, 95% CI: 0.95–1.50, P=0.132, Figure 2B). The ETV-treated group showed an initial increase in the median change in eGFR from baseline, followed by a gradual decline over the study period. Compared to the matched untreated group, the ETV-treated group significantly showed a lesser decrease in the median change from the baseline eGFR (Figure 3B and Table 4).

Comparison between the TDF-treated and untreated groups

The TDF-treated and untreated groups were compared using 1,201 PS-matched pairs. The baseline characteristics of the PS-matched cohort did not show significant difference except the ALT levels, HBeAg positivity, and HBV DNA levels (Table 2).

Over the 8,602 PYs of observation, 301 and 214 patients developed CKD progression, with incidence rates of 7.9 (95% CI: 7.0–8.8)/100 PYs and 4.5 (95% CI: 3.9–5.1)/100 PYs, respectively, in the TDF-treated and untreated groups, respectively (Table 3). The TDF-treated group had a significantly higher risk of CKD progression than the untreated group with an HR of 1.76 (95% CI: 1.47–2.10, P<0.001, Figure 2C). The TDF-treated group consistently showed a greater decrease in the median change from the baseline eGFR than the untreated group (P<0.05 for all, Figure 3C and Table 4).

Comparison between the TAF-treated and untreated groups

In the total of 426 PS-matched pairs, the baseline characteristics were comparable between the TAF-treated and untreated groups, except for the ALT levels, HBeAg positivity, and HBV DNA levels (Table 3). CKD progression occurred in 50 and 47 patients in the TAF-treated and untreated groups, respectively, during the 1,869 PYs of observation. The rate of CKD progression in the TAF-treated and untreated groups was 7.3 (95% CI: 5.4–9.6) and 4.0 (95% CI: 2.9–5.3), respectively. No significant difference was observed in the risk of CKD progression between the two groups (P=0.120, Figure 2D). Both groups had a continuous but not statistically significant decline in the median eGFR change from baseline during the study period (P>0.05 for all, Figure 3D and Table 4).

Table 3. Estimated crude incidence rates and hazard ratios in progression of chronic kidney disease stage ≥ 1

	N	Person-years	Event	Incidence rate, per 100 person-years (95% CI)	Hazard ratio, (95% CI)	P value
Entire cohort						
Untreated	6,162	27,392	1,225	4.5 (4.2–4.7)	1	
Treated	4,480	12,610	911	7.2 (6.8–7.7)	1.64 (1.51–1.80)	<0.001
Propensity score-matched cohort						
Untreated	1,996	7,556	331	4.4 (3.9–4.9)	1	
Treated	1,996	5,744	436	7.6 (6.9–8.3)	1.70 (1.47–1.97)	<0.001
Propensity score-matched cohort						
Untreated	755	2,725	152	5.6 (4.7–6.5)	1	
Entecavir	755	2,164	148	6.8 (5.8–8.0)	1.19 (0.95–1.50)	0.132
Propensity score-matched cohort						
Untreated	1,201	4,777	214	4.5 (3.9–5.1)	1	
TDF	1,201	3,825	301	7.9 (7.0–8.8)	1.76 (1.47–2.10)	<0.001
Propensity score-matched cohort						
Untreated	426	1,179	47	4.0 (2.9–5.3)	1	
TAF	426	690	50	7.3 (5.4–9.6)	1.40 (0.92–2.13)	0.120
Propensity score-matched cohort						
TAF	510	774	40	5.2 (3.7–7.0)	1	
Entecavir	510	1,526	92	6.0 (4.9–7.4)	1.36 (0.92–2.01)	0.118
Propensity score-matched cohort						
Entecavir	996	2,773	199	7.2 (6.2–8.1)	1	
TDF	996	2,781	251	9.0 (8.0–10.1)	1.26 (1.04–1.51)	0.016

Abbreviations: CI, confidence interval; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

Figure 2. Cumulative incidence of CKD progression

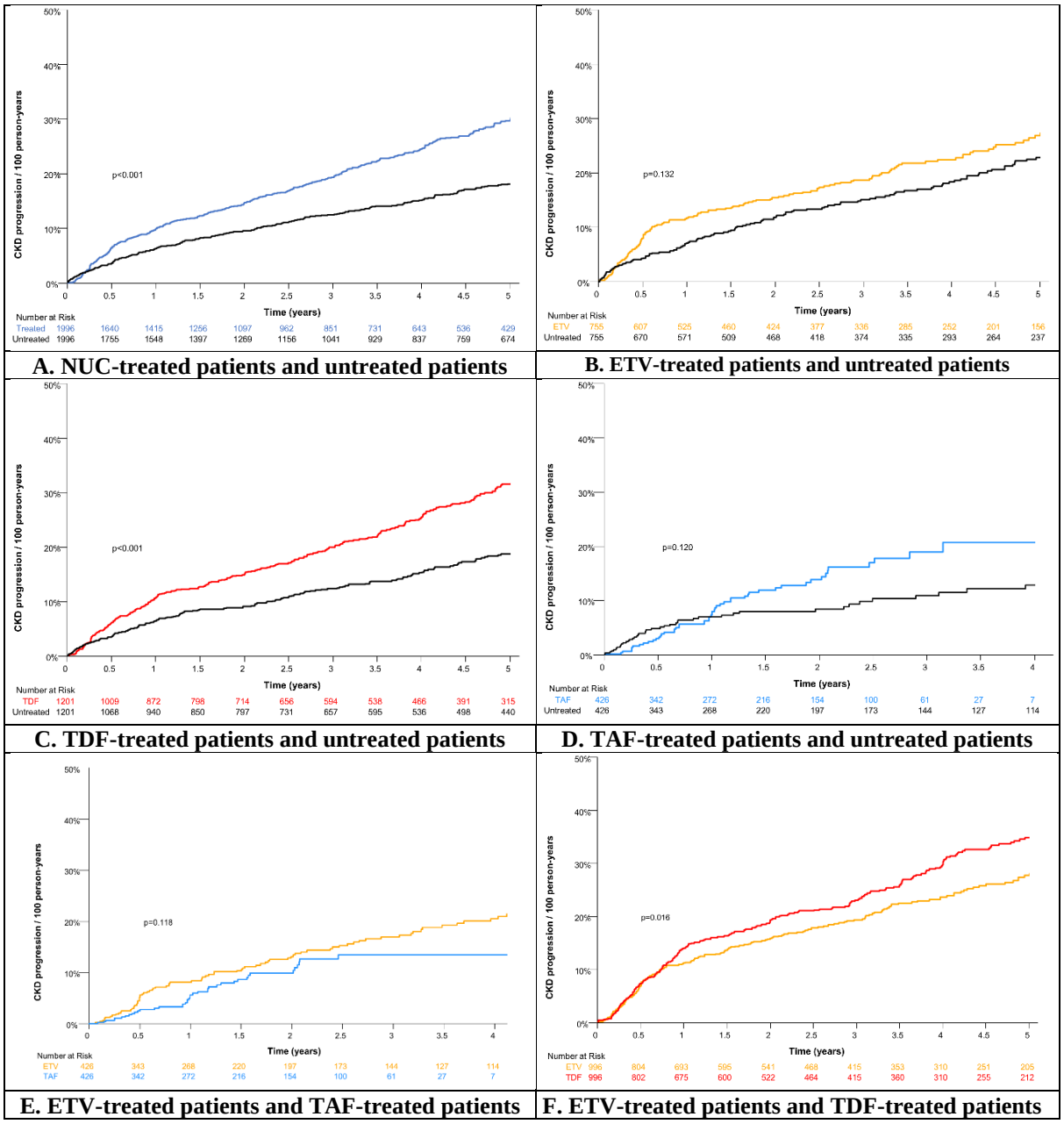


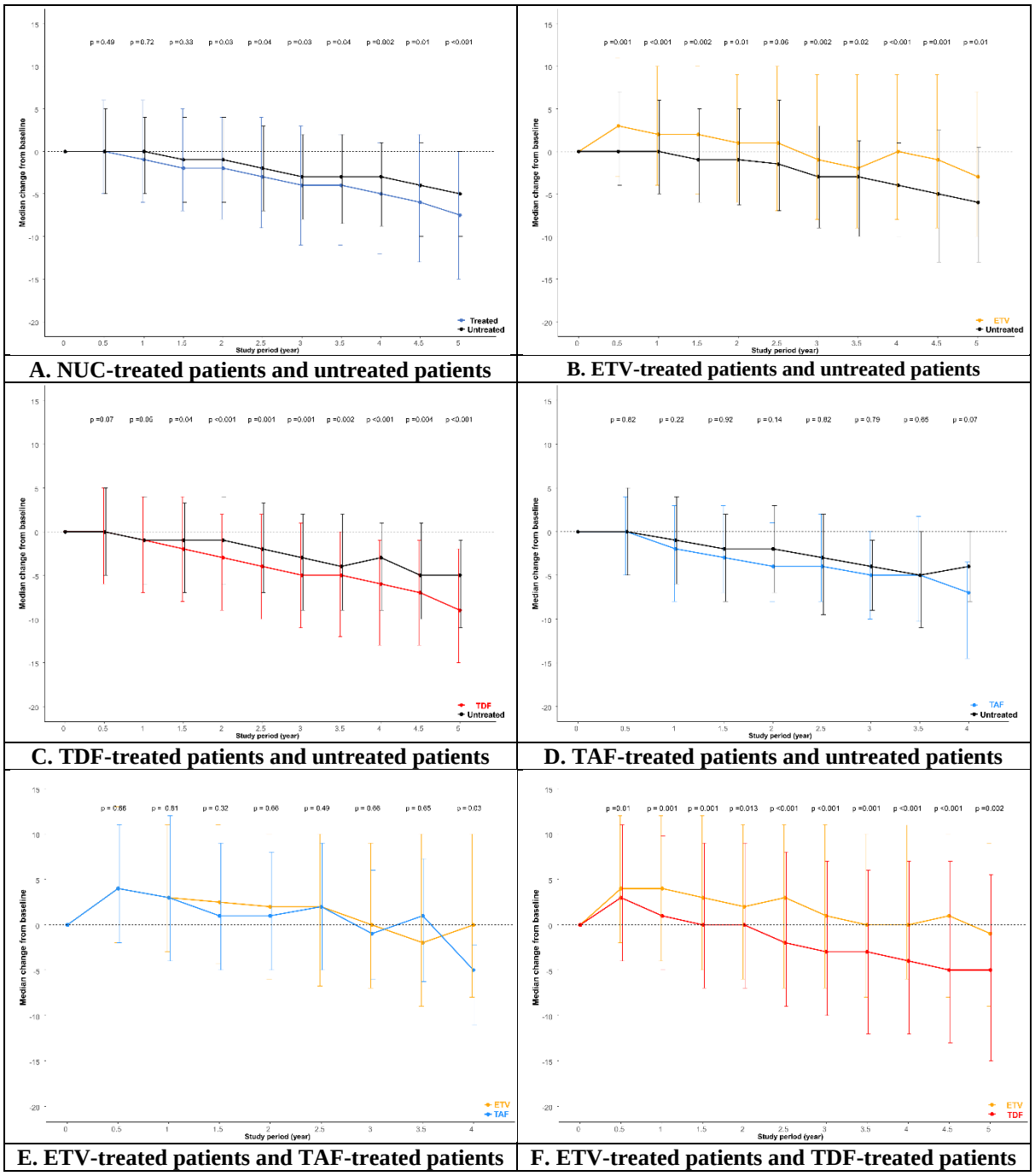
Table 4. Longitudinal changes in renal function during the study period

	N	Median (IQR)	N	Median (IQR)	P-value
	Treated (N=1,996)		**Untreated (N=1,996)**		
Change* at year 0.5	1,857	0 [-5, 6]	1,448	0 [-5, 5]	0.486
Change* at year 1	1,511	-1 [-6, 6]	1,109	0 [-5, 4]	0.716
Change* at year 1.5	1,352	-2 [-7, 5]	965	-1 [-6, 4]	0.330
Change* at year 2	1,226	-2 [-8, 4]	864	-1 [-6, 4]	0.031
Change* at year 2.5	1,103	-3 [-9, 4]	769	-2 [-7, 3]	0.040
Change* at year 3	1,008	-4 [-11, 3]	746	-3 [-8, 2]	0.029
Change* at year 3.5	872	-4 [-11, 2]	607	-3 [-8.5, 2]	0.043
Change* at year 4	788	-5 [-12, 1]	566	-3 [-8.75, 1]	0.002
Change* at year 4.5	691	-6 [-13, 2]	513	-4 [-10, 1]	0.010
Change* at year 5	630	-7.5 [-15, 0]	554	-5 [-10, 0]	<0.001
	ETV (N=755)		**Untreated (N=755)**		
Change* at year 0.5	682	3 [-3, 11]	565	0 [-4, 7]	0.001
Change* at year 1	559	2 [-4, 10]	429	0 [-5, 6]	<0.001
Change* at year 1.5	495	2 [-5, 10]	358	-1 [-6, 5]	0.002
Change* at year 2	460	1 [-6, 9]	328	-1 [-6.25, 5]	0.007
Change* at year 2.5	414	1 [-7, 10]	278	-1.5 [-7, 6]	0.063
Change* at year 3	385	-1 [-8, 9]	288	-3 [-9, 3]	0.002
Change* at year 3.5	333	-2 [-9, 9]	240	-3 [-10, 1.25]	0.018
Change* at year 4	300	0 [-8, 9]	222	-4 [-10, 1]	<0.001
Change* at year 4.5	255	-1 [-9, 9]	179	-5 [-13, 2.5]	0.001
Change* at year 5	219	-3 [-10, 7]	211	-6 [-13, 0.5]	0.010
	TDF (N=1,201)		**Untreated (N=1,201)**		
Change* at year 0.5	1,126	0 [-6, 5]	863	0 [-5, 5]	0.070
Change* at year 1	938	-1 [-7, 4]	672	-1 [-6, 4]	0.054
Change* at year 1.5	856	-2 [-8, 4]	600	-1 [-7, 3.25]	0.038
Change* at year 2	790	-3 [-9, 2]	536	-1 [-6, 4]	<0.001
Change* at year 2.5	733	-4 [-10, 2]	472	-2 [-7, 3.25]	0.001
Change* at year 3	693	-5 [-11, 1]	485	-3 [-9, 2]	0.001
Change* at year 3.5	637	-5 [-12, 0]	385	-4 [-9, 2]	0.002
Change* at year 4	581	-6 [-13, -1]	375	-3 [-9, 1]	<0.001
Change* at year 4.5	515	-7 [-13, -1]	339	-5 [-10, 1]	0.004
Change* at year 5	472	-9 [-15, -2]	386	-5 [-11, -1]	<0.001
	TAF (N=426)		**Untreated (N=426)**		
Change* at year 0.5	401	0 [-5, 4]	317	0 [-5, 5]	0.822
Change* at year 1	288	-2 [-8, 3]	187	-1 [-6, 4]	0.215
Change* at year 1.5	257	-3 [-7, 3]	151	-2 [-8, 2]	0.918
Change* at year 2	201	-4 [-8, 1]	127	-2 [-7, 3]	0.143
Change* at year 2.5	152	-4 [-8, 2]	99	-3 [-9.5, 2]	0.818
Change* at year 3	98	-5 [-10, 0]	97	-4 [-9, -1]	0.786
Change* at year 3.5	54	-5 [-10.3, 1.8]	71	-5 [-11, 0]	0.648
Change* at year 4	19	-7 [-14.5, -3.5]	55	-4 [-8, 0]	0.067
	ETV (N=510)		**TAF (N=510)**		
Change* at year 0.5	465	4 [-2, 13]	472	4 [-2, 11]	0.656
Change* at year 1	383	3 [-3, 11]	331	3 [-4, 12]	0.805
Change* at year 1.5	348	2.5 [-4.3, 11]	280	1 [-5, 9]	0.320
Change* at year 2	316	2 [-6, 10]	214	1 [-5, 8]	0.660
Change* at year 2.5	286	2 [-6.8, 10]	155	2 [-5, 9]	0.494
Change* at year 3	258	0 [-7, 9]	95	-1 [-6, 6]	0.656
Change* at year 3.5	229	-2 [-9, 10]	52	1 [-6.3, 7.3]	0.650
Change* at year 4	202	0 [-8, 10]	14	-5 [-11, -2.3]	0.026

	N	Median (IQR)	N	Median (IQR)	P-value
	ETV (N=996)		TDF (N=996)		
Change* at year 0.5	902	4 [-2, 12]	908	3 [-4, 3]	0.014
Change* at year 1	737	4 [-4, 12]	758	1 [-5, 1]	0.001
Change* at year 1.5	650	3 [-5, 12]	683	0 [-7, 0]	0.001
Change* at year 2	596	2 [-6, 11]	619	0 [-7, 0]	0.013
Change* at year 2.5	530	3 [-7, 11]	559	-2 [-9, 0]	<0.001
Change* at year 3	479	1 [-7, 11]	509	-3 [-10, -2]	<0.001
Change* at year 3.5	418	0 [-8, 10]	469	-3 [-12, -3]	0.001
Change* at year 4	370	0 [-6, 11]	421	-4 [-12, -4]	<0.001
Change* at year 4.5	315	1 [-8, 10]	367	-5 [-13, -5]	<0.001
Change* at year 5	276	-1 [-9, 9]	331	-5 [-15, -5]	0.002

*Indicates changes from the baseline.
Abbreviations: N, number of patients; IQR, interquartile range; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide

Figure 3. Longitudinal changes in eGFR during the study period



A. NUC-treated patients and untreated patients

B. ETV-treated patients and untreated patients

C. TDF-treated patients and untreated patients

D. TAF-treated patients and untreated patients

E. ETV-treated patients and TAF-treated patients

F. ETV-treated patients and TDF-treated patients

Comparison between the ETV-treated and TAF-treated groups

A total of 510 PS-matched pairs were used for comparing the ETV- and TAF-treated groups. No significant difference was observed in the baseline characteristics between the two groups (Table 5). In the ETV- and TAF-treated groups, 92 and 40 patients, respectively, experienced CKD progression with an incidence of 6.0 (95% CI: 4.9–7.4) and 5.2 (95% CI: 3.7–7.0), respectively (Table 3). The risk of CKD progression did not significantly differ between the two groups with a HR of 1.36 (95% CI: 0.92–2.01, P=0.118, Figure 2E). The median change in eGFR from baseline appeared to increase during the early period of observation, followed by a gradual decline during the final period of observation, but this change was not statistically significant (P>0.05 for all, Figure 3E and Table 4).

Comparison between the ETV-treated and TDF-treated groups

The ETV-treated and TDF-treated groups were compared using 996 PS-matched pairs. The baseline characteristics of the PS-matched cohort did not show significant difference (Table 6). Over the 5,554 PYs of observation, 199 and 251 patients developed CKD progression, with incidence rates of 7.2 (95% CI: 6.2–8.1)/100PYs and 9.0 (95% CI:8.0–10.1)/100PYs, respectively, in the ETV-treated and TDF-treated groups, respectively (Table 3). The TDF-treated group had a significantly higher risk of CKD progression than the untreated group with an HR of 1.26 (95% CI: 1.04–1.51, P=0.016, Figure 2F). The TDF-targeted group consistently showed a greater decrease in the median change from the baseline eGFR than the ETV-treated group (P<0.05 for all, Figure 3F and Table 4).

Improvement of Renal Function

Of the 8,506 patients who did not show CKD progression, 603 (7.1%) patients showed improvement in renal function as determined by CKD stages as a reference to the CKD stage at baseline. A total of 519 (86.1%) patients at baseline CKD stage 2 presented CKD stage 1 at their last visit (Table 7 and 8).

Table 5. Baseline characteristics of the study population in the propensity score-matched cohort comparing entecavir and tenofovir alafenamide

	PS-matched cohort		
	ETV (N=510)	**TAF (N=510)**	**ASD**
Demographic characteristics			
Age, years	52 [44, 58]	52 [45, 60]	0.082
Male, n (%)	274 (53.7)	283 (55.5)	0.035
Height, cm	164 [157, 172]	166 [159, 173]	0.103
Weight, kg	65 [56, 74]	66 [57, 76]	0.124
Body mass index, kg/m^2	24 [22, 27]	24 [22, 27]	0.033
Comorbidities			
Hypertension, n (%)	27 (5.3)	26 (5.1)	0.009
Diabetes, n (%)	22 (4.3)	28 (5.5)	0.055
Liver cirrhosis, n (%)	231 (45.3)	244 (47.8)	0.051
Laboratory findings			
Platelet count, $\times 10^3/\mu L$	175 [128, 226]	173 [137, 213]	0.054
ALT, IU/L	30 [19, 52]	37 [23, 64]	0.032
Total bilirubin, mg/dl	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.009
Prothrombin time, INR	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	0.018
Albumin, g/dl	4.0 [3.7, 4.2]	3.9 [3.7, 4.1]	0.010
Creatinine, mg/dl	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	0.029
eGFR, $ml/min/1.73m^2$	90 [87, 99]	90 [84, 97]	0.104
Total cholesterol, mg/dl	184 [154, 208]	179 [158, 204]	0.058
HBV DNA, $log_{10}IU/ml$	4.8 [2.3, 6.3]	4.8 [3.3, 6.5]	0.072
HBeAg positivity, n (%)	141 (37.7)	170 (38.6)	0.019

Table 6. Baseline characteristics of the study population in the propensity score-matched cohort comparing entecavir and tenofovir disoproxil fumarate

	PS-matched cohort		
	ETV (N=996)	**TDF (N=996)**	**ASD**
Demographic characteristics			
Age, years	54 [46, 60]	53 [45, 60]	0.003
Male, n (%)	577 (57.9)	587 (58.9)	0.020
Height, cm	165 [158, 172]	165 [158, 172]	0.022
Weight, kg	66 [57, 75]	66 [57, 74]	0.057
Body mass index, kg/m^2	24 [22, 27]	24 [22, 26]	0.093
Comorbidities			
Hypertension, n (%)	87 (8.7)	86 (8.6)	0.004
Diabetes, n (%)	117 (11.7)	112 (11.2)	0.016
Liver cirrhosis, n (%)	495 (49.7)	506 (50.8)	0.022
Laboratory findings			
Platelet count, × 10^3/μL	166 [114, 217]	169 [118, 215]	<0.001
ALT, IU/L	26 [17, 41]	29 [19, 48]	0.040
Total bilirubin, mg/dl	0.7 [0.5, 1.1]	0.7 [0.6, 1.1]	0.017
Prothrombin time, INR	1.1 [1.0, 1.1]	1.0 [1.0, 1.1]	0.009
Albumin, g/dl	3.9 [3.6, 4.2]	3.9 [3.6, 4.2]	0.015
Creatinine, mg/dl	0.8 [0.7, 0.9]	0.8 [0.7, 1.0]	0.027
eGFR, ml/min/1.73m^2	90 [83, 96]	90 [80, 96]	0.015
Total cholesterol, mg/dl	174 [146, 198]	171 [144, 195]	0.033
HBV DNA, $\log_{10}$IU/ml	2.8 [1.3, 5.3]	3.3 [2.0, 5.7]	0.098
HBeAg positivity, n (%)	340 (34.1)	336 (33.7)	0.008

Table 7. Improvement in renal function among patients without CKD progression

	No CKD progression (N=8,506)					
	Total (N=8,506)	**Treated (N=3,509)**	**Untreated (N=4,937)**	**ETV-treated (N=826)**	**TDF-treated (N=2,051)**	**TAF-treated (N=692)**
Improvement in eGFR	603 (7.1%)	333 (9.3%)	270 (5.5%)	98 (11.9%)	165 (8.0%)	70 (10.1%)
No change in CKD stages	7,903 (92.9%)	3,236 (90.7%)	4,667 (94.5%)	728 (90.1%)	1886 (92.0%)	622(89.9%)

Table 8. Migration to CKD stages between baseline and last visit among patients without CKD progression

	CKD stage at last visit among patients without progression to CKD (N=8,506)				
Baseline	**CKD satge1**	**CKD stage 2**	**CKD stage 3**	**CKD stage 4**	**CKD stage 5**
CKD stage 2	519				
CKD stage 3	6	66			
CKD stage 4	2	4	6		

Discussion

In this large-scale, real-world study, patients receiving NUC treatment exhibited a significantly higher risk of CKD progression than untreated patients. However, when stratified by the type of NUC, both ETV and TAF treatments were associated with risks of CKD progression comparable with that in the untreated group. In contrast, the TDF-treated group demonstrated a significantly greater risk of CKD progression than the untreated group. Moreover, no difference in the risk of CKD progression was observed between the ETV- and TAF-treated groups.

In a prior study, untreated patients with HBV exhibited an age-dependent loss in eGFR similar to that of the general population at approximately -1 mL/min/1.73 m^2 per year.(8) In accordance with this finding, untreated patients in our study displayed a gradual decrease in renal function with a median decline in eGFR of 1 mL/min/1.73 m^2 annually during the study period. This consistency with prior findings suggests that untreated patients in the current study can serve as a suitable reference for comparisons with patients treated with NUCs.

Previous studies have shown that NUC treatment is associated with greater renal impairment than that observed in untreated patients.(8, 9) Consistent with this, in the present study, patients receiving NUC treatment had a 1.7-fold higher risk of CKD progression than untreated patients. However, this elevated risk of CKD progression in treated patients was predominantly attributed to those receiving TDF. Only TDF-treated patients exhibited a 1.76-fold higher risk of CKD progression than untreated patients. There was no significant difference in the risk of CKD progression for ETV- or TAF-treated patients when compared with untreated patients, aligning with the findings of previous studies from the U.S. and Hong Kong.(8, 9) Although TDF is a first-line preferred agent for CHB treatment according to international guidelines, the risk of nephrotoxicity increases with long-term treatment. As a result, international guidelines recommend ETV or TAF over TDF for patients at risk of renal disease.(2-4)

Interestingly, a recent study by Lee et al. reported that ETV (3.6/1,000 PYs) was associated with a significantly increased risk of CKD progression (1.1/1,000 PYs) using the same CKD progression definition as ours. However, the rates of CKD progression stage ≥1 in Lee et al.'s study for the ETV-treated and untreated groups were 36/100 PYs and 11/100 PYs, respectively. These rates are notably

high when expressed in the same incidence unit (per 100 PYs) as in previous reports and in the present study. In addition, despite having a higher rate of CKD progression than the untreated group in our study (7.6/100 PYs), the untreated group in Lee et al.'s study did not exhibit the anticipated age-dependent decrease in eGFR during the study period. In our study, the ETV-treated group experienced a slight increase in eGFR shortly after initiating treatment, followed by a consistent decline in eGFR over the study period. This interesting pattern was also observed in a previous study.(11) We postulate that patients treated with ETV might be more predisposed to renal dysfunction, leading to their selection for ETV over TDF at the onset of treatment, especially given the lower baseline eGFR in the ETV-treated group than in the TDF-treated group. Consequently, controlling active inflammation with ETV might temporarily restore renal function to its actual baseline value, followed by the expected gradual decline in renal function observed in the untreated and other NUC groups. Therefore, although there was a significant difference between ETV-treated and untreated patients in the median changes in eGFR throughout the study period, the CKD progression rate did not significantly differ between the two groups.

Another intriguing study by Jung et al. reported that ETV (19.9/100 PYs) was associated with a significantly higher risk of CKD progression than TAF (5.1/100 PYs).(12) However, using the same definition of CKD progression, the TAF-treated group (5.2/100 PYs) in our study showed a risk of CKD progression comparable to that in the ETV-treated group (6.0/100 PYs). Despite the similar risk of CKD progression in the TAF-treated groups in both studies, the significantly different risk observed in the ETV-treated groups in both studies warrants further investigation in future research.

TAF is known to be safe for use even in patients with renal dysfunction. The diminished renal function resulting from TDF can also be restored after switching to TAF, both in treatment-naïve and treatment-experienced patients.(15-17) Indeed, in our study, TAF did not further impair renal function when compared with both ETV and no NUC treatment. There have been some recent conflicting results regarding the CKD progression risk in TAF-treated patients. The rate of CKD progression in the TAF-treated group was 5.1/100 PYs in the aforementioned paper by Jung et al., which aligns closely with our findings. However, other studies from the same group reported a much higher incidence of CKD progression, with rates of 31/100 PYs and 39/100 PYs.(13, 18) These discrepancies should also be further explored in future research, possibly in different countries.

A strength of our study is the inclusion of a large cohort of treated patients, especially encompassing TAF-treated and untreated patients. To the best of our knowledge, our study represents the largest hospital-based CHB cohort to evaluate the longitudinal change in renal function in NUC-treated patients compared with untreated patients. The comparison with untreated patients as a reference enabled us to discern a robust serial trend in renal function after NUC treatment initiation. We also conducted a comprehensive comparison of the risk of CKD progression based on treatment type, noting that previous reports only focused on head-to-head comparisons. In addition, we maintained consistency with previous studies by using the same definition of CKD progression as the primary outcome.

However, our study does have some limitations. First, as a retrospective single-center study based on observational data, potential biases and confounders could have influenced the analysis. Second, although we employed PS matching analysis to minimize potential biases, unmeasured confounders remained unadjusted in this analysis. Furthermore, ALT, total bilirubin, and HBV DNA levels were not incorporated into the PS calculation for matching between NUC-treated, ETV-treated, TDF-treated and untreated groups. As outlined in our methods, NUC-treated and untreated patients inherently differed in their baseline characteristics, such as ALT, total bilirubin, and HBV DNA levels, which comprised the criteria for NUC treatment. With these variables putting into the PS calculation, sufficient PS-matched pairs would not be generated. These differences may also contribute to the renal function deterioration, which is another limitation of our study. However, when comparing ETV- and TAF-treated patients, and comparing ETV- and TDF-treated patients, these variables were included in the PS matching analysis. TAF was approved in Korea in late 2017. As a result, the follow-up period for patients receiving TAF was shorter than that for patients receiving other NUCs or that for those who were untreated. Thus, when analyzing TAF-treated patients, we assessed serial renal function up to four years from the start of treatment due to the limited number of TAF-treated patients beyond this period. Nonetheless, previous studies on TAF have reported outcomes spanning only up to two years, which underscore the robustness of our study. Given the definition of CKD progression is based on cut-off of CKD stages, patients whose eGFR was very close to the lower margin of CKD stage category may be vulnerable to fulfill the primary outcome, CKD progression at least ≥1 stage, even with a minimal change of their eGFR during the study period. This might overestimate the risk of CKD progression in these patients. However, previous studies also used same definition of the primary outcome and we also analyzed longitudinal changes in eGFR values itself at each observational time.

Conclusion

In conclusion, among patients with CHB, NUC treatment was associated with a significantly increased risk of CKD progression that was primarily driven by TDF treatment. Both ETV- and TAF-treated patients exhibited comparable risks of CKD progression when compared with untreated patients. There was no significant difference in the risk of CKD progression between ETV- and TAF-treated patients. As patients receiving NUC treatment age, they become more susceptible to developing other comorbidities that can adversely affect renal function. Consequently, periodic monitoring of renal function is essential for these patients.

References

1. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med. 2004;351(15):1521-31.
2. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-99.
3. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-98.
4. Korean Association for the Study of the L. KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol. 2022;28(2):276-331.
5. Oh H, Jun DW, Lee IH, Ahn HJ, Kim BO, Jung S, et al. Increasing comorbidities in a South Korea insured population-based cohort of patients with chronic hepatitis B. Aliment Pharmacol Ther. 2020;52(2):371-81.
6. Chen YC, Su YC, Li CY, Hung SK. 13-year nationwide cohort study of chronic kidney disease risk among treatment-naïve patients with chronic hepatitis B in Taiwan. BMC Nephrol. 2015;16:110.
7. Chen YC, Su YC, Li CY, Wu CP, Lee MS. A nationwide cohort study suggests chronic hepatitis B virus infection increases the risk of end-stage renal disease among patients in Taiwan. Kidney Int. 2015;87(5):1030-8.
8. Udompap P, Kim D, Ahmed A, Kim WR. Longitudinal trends in renal function in chronic hepatitis B patients receiving oral antiviral treatment. Aliment Pharmacol Ther. 2018;48(11-12):1282-9.
9. Wong GL, Chan HL, Tse YK, Yip TC, Lam KL, Lui GC, et al. Chronic kidney disease progression in patients with chronic hepatitis B on tenofovir, entecavir, or no treatment. Aliment Pharmacol Ther. 2018;48(9):984-92.
10. Jung CY, Kim HW, Ahn SH, Kim SU, Kim BS. Tenofovir is Associated With Higher Risk of Kidney Function Decline Than Entecavir in Patients With Chronic Hepatitis B. Clin Gastroenterol Hepatol. 2022;20(4):956-8.e2.
11. Chon YE, Park SY, Kim SU, Hong HP, Lee JS, Lee HW, et al. Long-term renal safety between patients with chronic hepatitis B receiving tenofovir vs. entecavir therapy: A multicenter study. J Viral Hepat. 2022;29(4):289-96.
12. Jung CY, Kim HW, Ahn SH, Kim SU, Kim BS. Higher risk of kidney function decline with entecavir than tenofovir alafenamide in patients with chronic hepatitis B. Liver Int. 2022;42(5):1017-26.
13. Lee JS, Jung CY, Lee JI, Ahn SH, Kim BS, Kim SU. Comparison of decline in renal function between patients with chronic hepatitis B with or without antiviral therapy. Aliment Pharmacol Ther. 2023;58(1):99-109.
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
15. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68(4):672-81.
16. Ogawa E, Nakamuta M, Koyanagi T, Ooho A, Furusyo N, Kajiwara E, et al. Switching to tenofovir alafenamide for nucleos(t)ide analogue-experienced patients with chronic hepatitis B: week 144 results from a real-world, multi-centre cohort study. Aliment Pharmacol Ther. 2022;56(4):713-22.

17. Byun KS, Choi J, Kim JH, Lee YS, Lee HC, Kim YJ, et al. Tenofovir Alafenamide for Drug-Resistant Hepatitis B: A Randomized Trial for Switching From Tenofovir Disoproxil Fumarate. Clin Gastroenterol Hepatol. 2022;20(2):427-37 e5.
18. Jung CY, Kim HW, Lee JI, Lee HW, Ahn SH, Kim SU, et al. Similar risk of kidney function decline between tenofovir alafenamide and besifovir dipivoxil maleate in chronic hepatitis B. Liver Int. 2022;42(11):2408-17.

Abstract

Background: Patients with chronic hepatitis B (CHB) on nucleos(t)ide analogues (NUCs) often experience renal function decline. Conflicting results regarding the impact of NUC use and renal function have recently been reported. We aimed to examine longitudinal changes in renal function according to the NUC treatment type compared with untreated patients.

Methods: From 2014 to 2022, 10,642 patients with CHB were retrospectively analyzed. The primary outcome was chronic kidney disease (CKD) progression, which was defined as a minimum one-stage elevation. Propensity score (PS) matching was employed for outcome comparisons.

Results: In the PS-matched cohort of 1,996 pairs, the NUC-treated group (7.6/100 person-years [PYs]) had a significantly higher CKD progression risk than the untreated group (4.4/100 PYs), with a hazard ratio (HR) of 1.70 (P<0.001). The tenofovir disoproxil fumarate (TDF)-treated group (7.9/100 PYs) showed a 1.76-fold increased CKD progression risk compared with the untreated group (4.5/100 PYs) in the PS-matched cohort (P<0.001). Both the entecavir (ETV)- and tenofovir alafenamide (TAF)-treated groups showed CKD progression risks comparable to those of the untreated group in the PS-matched cohorts of 755 and 426 pairs, respectively (P=0.132 and P=0.120, respectively). No significant CKD progression risk was found between the ETV- (6.0/100 PYs) and TAF-treated (5.2/100PYs) groups in the PS-matched cohort of 510 pairs (P=0.118).

Conclusion: NUC-treated patients, especially those on TDF, faced a higher CKD progression risk than untreated patients. ETV- and TAF-treated patients presented comparable CKD progression risks to untreated patients. No difference was observed between ETV and TAF in the risk of CKD progression.