

Supplementary Material: Systematic Review with Meta-Analysis: Comparison of the Risk of Hepatocellular Carcinoma in Antiviral-Naive Chronic Hepatitis B Patients Treated with Entecavir versus Tenofovir: The Devil in the Detail

Hyunwoo Oh, Hyo Young Lee, Jihye Kim and Yoon Jun Kim

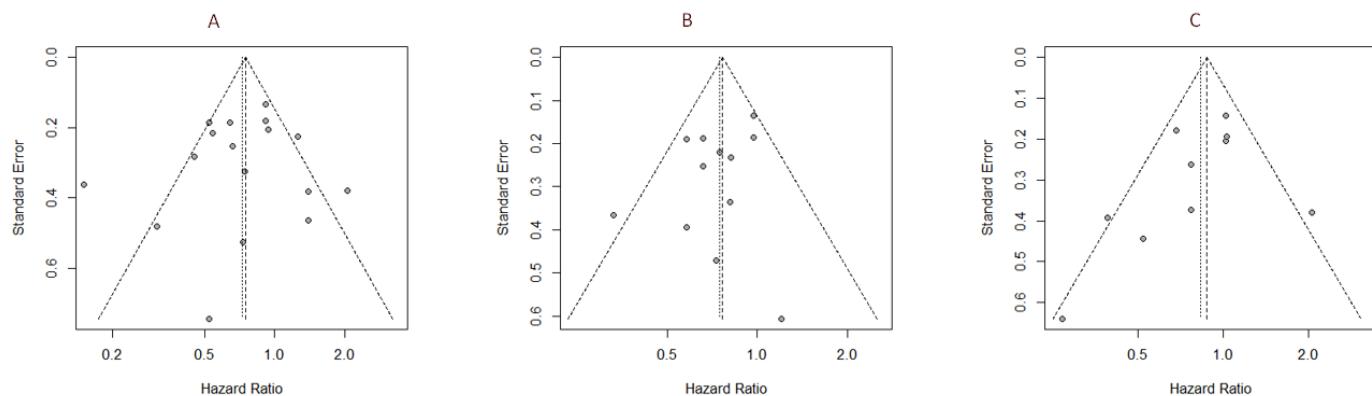


Figure S1. Analysis of publication bias. Using the AS-Thompson's test for publication bias, no significant asymmetry is seen in the funnel plots ($P > 0.1$) for Pooled analysis of representative HRs presented in individual papers (A), adjusted HR (B), and PS-matched HR (C).

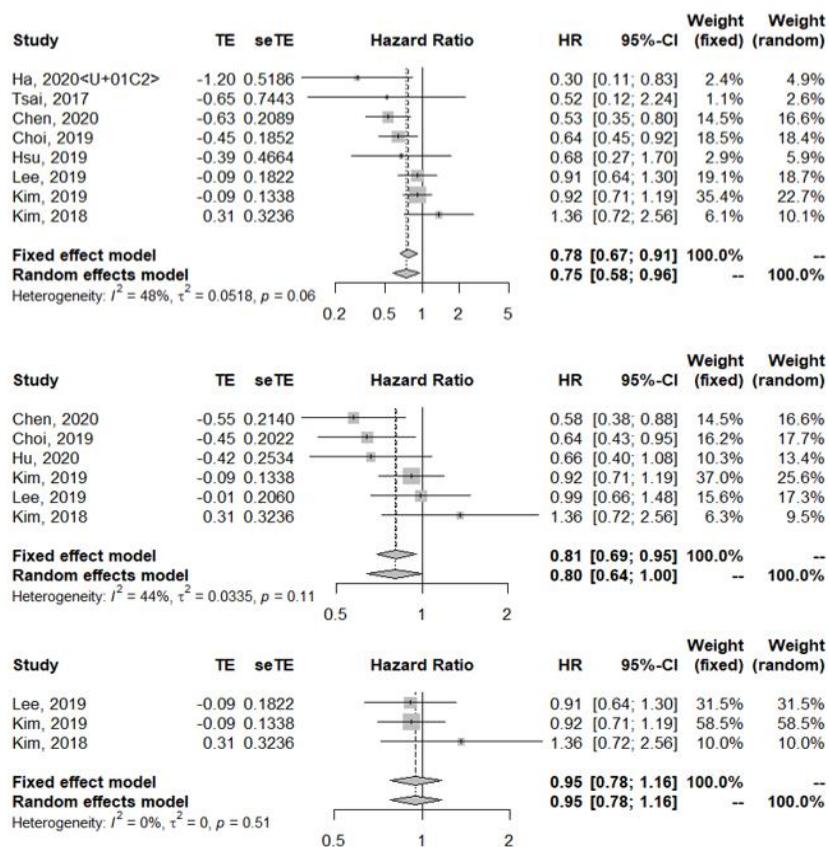


Figure S2. Pooled analysis of representative HRs presented in individual papers/multivariable-adjusted HR/propensity score-matched HR in the cirrhotic subcohort.

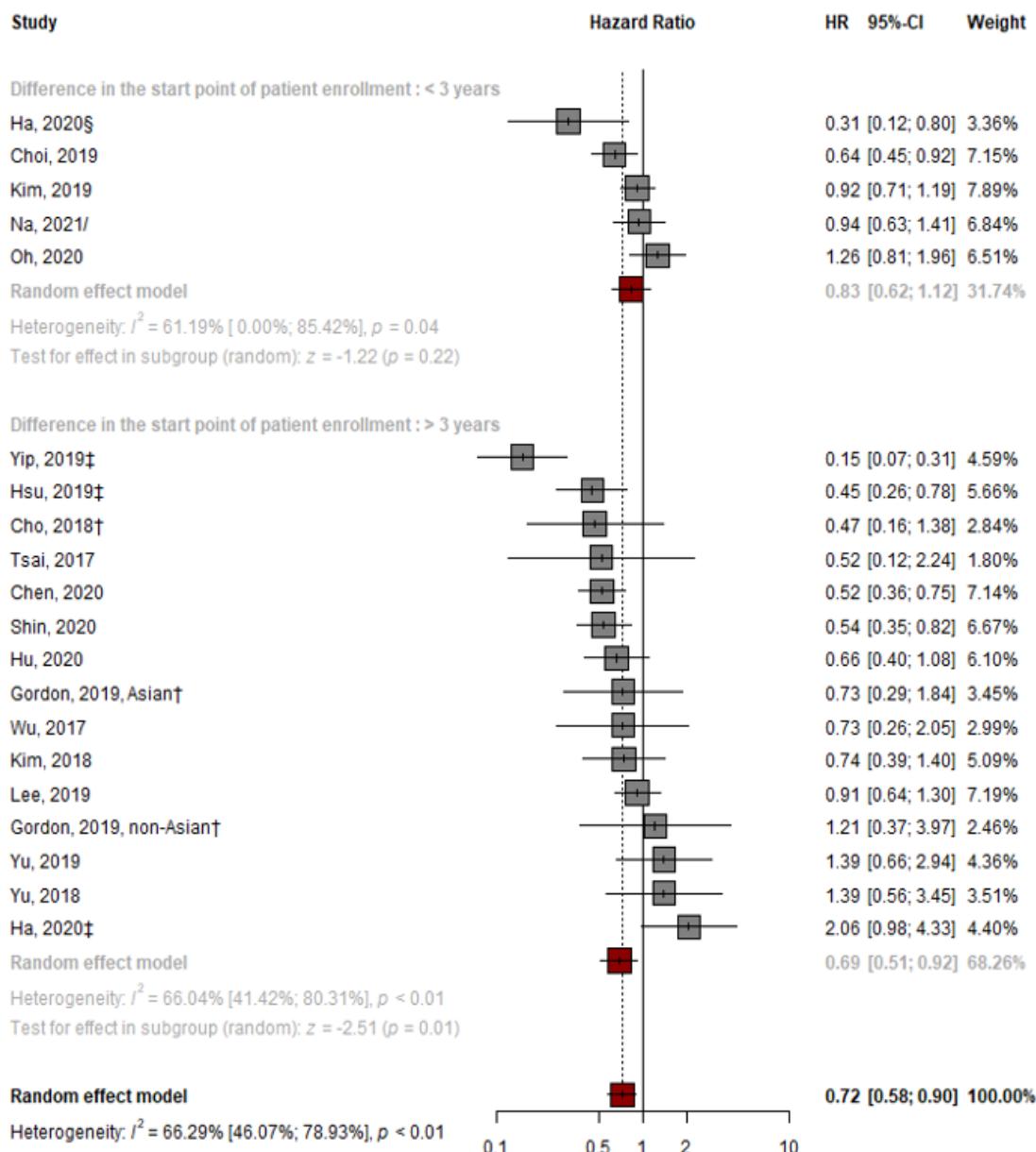


Figure S3. Pooled HR from a subgroup analysis according to the starting point. † abstract; ‡ suggest outcomes from competing risk analysis; § Ha from CHA Bundang Medical Center, CHA University; / from unadjusted cohort at the time of CVR.

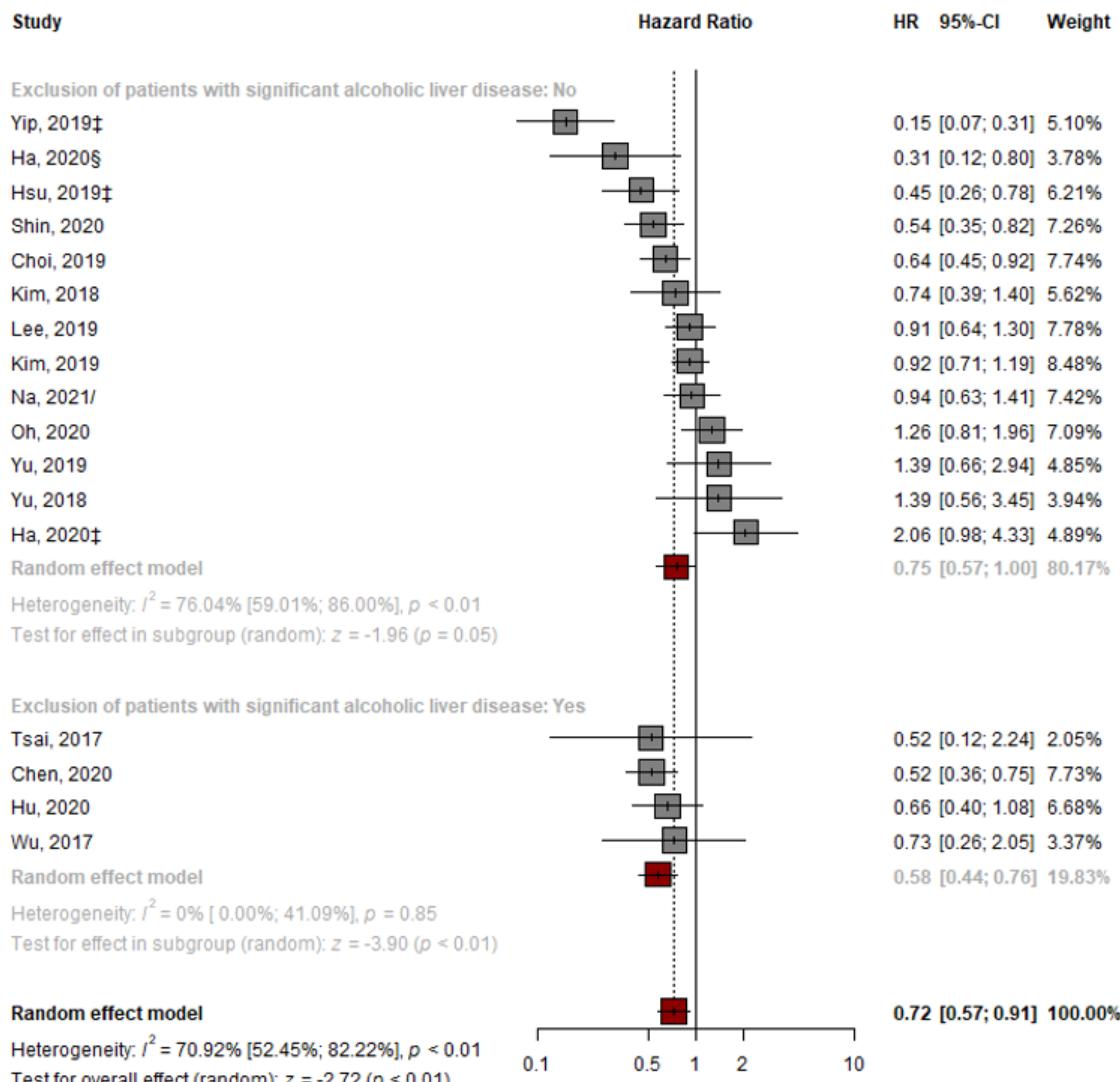


Figure S4. Pooled HR from a subgroup analysis after excluding alcoholic liver disease. ‡ suggest outcomes from competing risk analysis; § Ha from CHA Bundang Medical Center, CHA University; / from unadjusted cohort at the time of CVR.

Table S1. Search strategies.

Data Base	Search Strategy
Medline	1. (tenofovir) OR (tenofovir [tw]) 2. (entecavir) OR (entecavir [tw]) 3. (hepatocellular carcinoma) OR (hepatocellular carcinoma [tw]) 4. 1 AND 2 5. 3 AND 4
EMBASE	1. ('tenofovir'/exp OR 'tenofovir':ab,ti OR 'tenofovir'/de) AND [embase]/lim 2. ('entecavir'/exp OR 'entecavir':ab,ti OR 'entecavir'/de) AND [embase]/lim 3. ('hepatocellular carcinoma'/exp OR 'hepatocellular carcinoma':ab,ti OR 'hepatocellular carcinoma'/de) AND [embase]/lim 4. 1 AND 2 5. 3 AND 4 1. tenofovir:ti,ab,kw 2. entecavir:ti,ab,kw
Cochrane	3. hepatocellular carcinoma:ti,ab,kw 4. 1 AND 2 5. 3 AND 4

Table S2. Newcastle-Ottawa scale for non-randomized studies (Abstracts were excluded from assessment.).

Bias	Choi 2019	Kim 2018	Shin 2020	Kim 2019	Lee 2019	Tsai 2017	Yip [‡] 2019	Yu 2018	Yu 2019	Wu 2017	Hsu [‡] 2019	Ha [§] 2020	Oh 2020	Ha [‡] 2020	Hu 2020	Chen 2020	Na [/] 2021
Selection																	
1) Representativeness of the exposed cohort	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
2) Selection of the non exposed cohort	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
3) Ascertainment of exposure	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
4) Demonstration that outcome of interest was not present at start of study	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Comparability																	
1) Comparability of cohorts on the basis of the design or analysis	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
2) Comparability of cohorts on the control of variables	★	★	★	★	★	★	★	-	-	-	★	★	★	★	★	★	★
Outcome																	
1) Assessment of outcome	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
2) Was follow-up long enough for outcomes to occur (mean ≥ 5 yrs, each arm)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	★	-	-
3) Adequacy of follow up of cohort (Follow up rate ≥ 80%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

[‡] suggest outcomes from competing risk analysis; [§] Ha from CHA Bundang Medical Center, CHA University; [/] from unadjusted cohort at the time of CVR. - The research isn't according with this point, based on the Newcastle-Ottawa scale; ★, The research is according with this point, based on the Newcastle-Ottawa scale.

Table S3. Adjusted variables for Cox regression analyses for risk of HCC development in the included articles.

Author	Year	Age	Sex	Cirrosis	HBeAg	HBV_DNA	AST	ALT	Alb	Bil	Cr	AFP	PT	PLT	DM	HTN	Additional variables
Choi	2019	●	●	●	●	●	Log *	●				●	●	●			Ascites *, CTP, Virologic response (HBV-DNA < 60 at 1 year of treatment) *
Kim,	2018	●	●	●	●		●	●	●				●	●			Duration of treatment *
Shin,	2020	●	●	●	●	●		●	●			●	●	●			Adherence *, VR12 *, MVR *
Kim	2019																NA
Lee	2019	●	○	○	○	●	○	○	○	○	○	○	○	●	●	●	Alcohol, BMI, APRI, FIB-4 *, CTP, Varix (Y/N), GGT, Treatment initiation
Tsai	2017	●	○		○	●			○	○	○	○	○	○	○	○	BMI, Metformin use, Statin use *, Anti-PLT use, HBV genotype, HBsAg titer, CTP, Ascites, Variceal bleeding (Y/N) *, MELD, Virologic response
Yip	2019 ‡	●	●	●	●	○		●	●	○		○	●	○	○		Enrolled calendar year of patients *
Yu	2018	●	●	●	○	○		○	●	●		○	●	○			Virologic response (HBV-DNA negative at 12 months of AVT)
Yu	2019	●	●	●	○	○		○	●	○		○	○	○			Suboptimal response/virologic failure after AVT
Wu	2017	○	○	○	●	●	○	○		○	○	○	○	○	○		FIB-4, HBsAg titer *, HBV Genotype
Hsu	2019 ‡	●	●	●	○	○	○	○	●	○	○	●	○	●	●		Region *, Decompensation, BMI, FIB-4
Ha	2020 §	○	○	○	○	○		○	○	○	○	○	○	○	○		BMI, CTP, Biochemical/Serological/Virological response, SVR
Oh	2020	●	○	●	●	●			●	○	GFR	○	●	●	○	●	CKD
Ha	2020 ‡	●	●	○	○	●	○	○	●	○	○	○	●	●	○		Alcohol, HBsAg titer
Hu	2020	○	-		○		○	○	○			●	●	●			FIB-4, HCC family history *, Varix *
Chen	2020	●	●	-	○	○	○	○	●	○	GFR	○	○	●	●	○	(NA experience) Decompensation *, CTP, FIB-4, APRI
Na	2021 /	●	●	●	○	●		●	●	●	GFR	●	●	●	●		Time to CVR, Cholesterol *

○ ; variables for univariate Cox regression only, ●, * ; variables for multivariate Cox regression; ‡ suggest outcomes from competing risk analysis; § Because of the low number of events (HCC), authors did not performed multivariable analyses; / from unadjusted cohort at the time of CVR Cr, creatinine; GFR, glomerulus filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; PLT, platelet; AFP, alpha fetoprotein; BMI, body mass index; APRI, AST/platelet ratio index; FIB-4, fibrosis-4 index; CTP, Child-Turoctte-Pugh; MELD, model for end-stage liver disease; GGT, gamma-glutamyl transferase; VR12, virologic response at 12 months; MVR, maintained virologic response; SVR, sustained virologic response; CVR, complete virologic response; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; NA, Nucleos(t)ide analogue;

Table S4. Adopted variables for propensity score matching analysis to reduce selection bias and the effect of potential confounders in the included articles.

Author	Year	Age	Sex	Cirrosis	HBeAg	HBV_DNA	AST	ALT	Alb	Bil	Cr	AFP	Pt	PLT	DMD	MHTN	Additional Variables
Choi	2019	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	Ascites, CTP, CU-HCC, GAG-HCC, PAGE-B, REACH-B
Kim,	2018	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	GAG-HCC, CU-HCC, REACH-B, PAGE-B
Shin,	2020	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	GAG-HCC, CU-HCC, REACH-B, PAGE-B
Kim	2019	○	○	○	○				○	○		○	○	○	○	○	
Lee	2019	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(severity of underlying liver disease), Alcohol, BMI, APRI, FIB-4, CTP, Varix (Y/N), GGT
Yip	2019‡	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	Ascites, Encephalopathy, Renal replacement therapy, Enrolled calendar year of patients
Wu	2017	○	○	○	○												
Hsu	2019 †	○	○	○	○	○	○				○	○					Country, Decompensation
Ha	2020 §	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	CTP, GAG-HCC, CU-HCC, PAGE-B, SVR
Oh	2020	○	○	○	○	○			○	○	GFR	○	○	○	○	○	CKD, Decompensation, CTP, MELD, FIB-4
Ha	2020 ‡	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	Alcohol, Enrolled calendar year of patients, HBsAg titer
Hu	2020	○	-						○	○							
Chen	2020	○	○	-	○	○	○	○	○	○	GFR	○	○	○	○	○	(NA experience) Decompensation, FIB-4, APRI
Na	2021 /	○	○	○	○	○	○	○	○	GFR	○	○					Time to CVR, Cholesterol

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; PLT, platelet; AFP, alpha fetoprotein; BMI, body mass index; APRI, AST/platelet ratio index; FIB-4, fibrosis-4 index; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; GGT, gamma-glutamyl transferase; VR12, virologic response at 12 months; MVR, maintained virologic response; SVR, sustained virologic response; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; CU-HCC, Chinese University HCC score; GAG-HCC, Guide With Age, Gender, HBV DNA, Core Promoter Mutations, and Cirrhosis-HCC score; PAGE-B, platelet age gender B score; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B score; ‡ suggest outcomes from competing risk analysis; § Ha from CHA Bundang Medical Center, CHA University; / from unadjusted cohort at the time of CVR.

Table S5. Statistical methods used in the included articles.

Author Year	Adopted Method for Variable Selection in Cox Regression	Cut Off of P Value to Select the Variables for Multivariate Model	Propensity Score Matching Method	IPTW	Competing Risk Analysis (Model by Fine and Gray)	Multiple Imputation for Missing Data
Choi 2019	-	NA	Nearest-neighbor 1:1 matching Caliper size of 0.1	○	○	0.02% to 3.7%
Kim, 2018	-	0.2	Caliper size of 0.2	-	-	-
Shin, 2020	-	-	Caliper size of 0.1	○	○	○
Kim 2019	-	-	○	○	-	-
Lee 2019	(Sandwich covariance matrix estimation)	-	Nearest-neighbor 1:1 matching Caliper size of 0.2	○	○	0% to 4.6%
Tsai 2017	Stepwise method	-	-	-	-	-
Yip 2019 ‡	Backward elimination	-	Nearest-neighbor 1:1 matching	○	○	HBeAg status (19.7%) HBV DNA level (35.7%) ALT (4.2%) Albumin (4.0%) Total bilirubin (4.5%) INR (21.8%) Platelet (7.2%) Creatinine (10.6%)
Yu 2018	-	-	-	-	-	-
Yu 2019	Backward deletion	-	-	-	-	-
Wu 2017	-	-	Nearest available matching Caliper size NA	-	-	-
Hsu 2019 ‡	Stepwise approach	-	Caliper 0.2	-	○	-
Ha 2020 §	-	-	○	○	-	Platelet (2.5%) Albumin (1.7%) Total bilirubin (1.2%) PT (2.2%) Creatinine (1.7%)
Oh 2020	-	-	Nearest-neighbor 1:1 matching Caliper size NA	-	-	-
Ha 2020 ‡	-	-	Nearest-neighbor 1:1 matching Caliper size NA	○	○	-
Hu 2020	Stepwise selection	-	Caliper size of 0.15 and 0.2	○	-	No missing data
Chen 2020	Forward method	0.25	Nearest-neighbor 1:1 matching Caliper size of 0.2	○	-	○
Na 2021 /	-	-	Nearest-neighbor 1:1 matching Caliper size of 0.1	○	-	eGFR in 7 (0.5%) platelet 19 (1.4%) HBeAg in 47 (3.5%) PT in 51 (3.8%) HBV DNA in 63 (4.7%)

‡ suggest outcomes from competing risk analysis; § Ha from CHA Bundang Medical Center, CHA University; / from unadjusted cohort at the time of CVR., ○, authors used statistical techniques in first row, IPTW, Inverse Probability Treatment Weighting; NA, not available.

Table S6. Characteristics after propensity score matching analysis in the included studies.

Author Year Country	Cirrhosis (%)	Patients (n)		Age (mean (\pm SD))	Sex (Male%)	HBV_DNA	HBeAg Positive (%)
		TDF ETV	ETV	TDF ETV	TDF ETV	(log10) (IU/mL)	
Choi 2019 Korea	505 (58.1) 511 (58.8)	869 869		48.8 \pm 10.4 48.8 \pm 10.4	540 (62.1) 519 (59.7)	6.5 (5.6, 7.7) 6.5 (5.3, 7.7)	481 (55.4) 479 (55.1)
Kim, 2018 Korea	156 (44.1) 169 (47.7)	354 354		50 \pm 11 50 \pm 11	223 (63.0) 220 (62.1)	6.2 \pm 1.5 6.2 \pm 1.4	223 (63.0) 232 (65.5)
Shin, 2020 Korea	282 (47.88) 276 (46.86)	589 589		50 \pm 11 50 \pm 11	358 (60.8) 365 (320.)	6.22 (4.99–7.63) 6.11 (4.99–7.44)	354 (60.1) 365 (61.97)
Kim 2019 Korea	400 (31.3) 394 (30.8)	1278 1278		48.2 \pm 12.0 48.6 \pm 11.4	913 (64.6) 889 (59.9)	5.55 \pm 2.09 5.62 \pm 2.11	640 (50.1) 640 (50.1)
Lee 2019 Korea	464 (33.87) 465 (33.94)	1370 1370		46.92 (11.13) 42.9 \pm 12.7	798 (58.25) 806 (58.83)	6.39 (5.34, 7.49) 6.51 (5.30, 7.71)	807 (58.91) 814 (59.42)
Yip 2019 ‡	37 (3.1)	1200		44.4 \pm 13.1	587 (48.9)	4.8 \pm 2.7	625 (52.1)
Hongkong	NA (3.6)	4636		42.9 \pm 12.7	NA (48.9)	4.8 \pm 2.8	NA (53.5)
Wu 2017	29(27.4)	106		47.1 \pm 12.1	74 (69.8)	7.35 \pm 0.7	50(47.1)
Taiwan	57(26.9)	212		46.3 \pm 13.2	230 (73.5)	7.26 \pm 0.73	100(47.2)
Hsu 2019 ‡	105 (20.19)	520		44.88 \pm 0.55	338 (65.0)	5.07 \pm 0.10	177 (34.0)
Worldwide	107 (20.58)	520		44.12 \pm 0.54	354 (68.1)	5.0 \pm 0.10	187 (36.0)
Ha 2020 ‡ Korea	39 (9) 39 (9)	298 298		48 \pm 14 48 \pm 16	179 (60) 181 (61)	6.29 (2.51) 6.43 (2.77)	174 (58) 161 (54)
Oh 2020 Korea	224 (43.4) 238 (46.1)	516 516		49.0 \pm 9.4 49.2 \pm 12.6	325 (63.0) 319 (61.8)	6.4 [5.4, 7.5] 6.4 [5.4, 7.5]	311 (60.3) 314 (60.9)
Ha 2020 § Korea	56 (33.3) 58 (34.5)	168 168		45.0 \pm 11.6 45.4 \pm 10.9	94 (56.0) 100 (59.5)	7.74 (6.48, 8.74) 7.82 (6.85, 8.64)	109 (64.9) 111 (66.1)
Hu 2020	100%	157		58.6 \pm 11.0	115 (73.2)		28 (17.6)
Taiwan		607		58.8 \pm 10.8	442 (72.8)		114 (18.7)
Na 2021 / Korea	299 (52.5) 299 (52.5)	570 570		50 (44, 57) 50 (44, 56)	334 (58.6) 339 (59.5)	5.7 (4.5, 6.8) 5.7 (4.6, 6.8)	202 (35.4) 177 (31.0)

‡ suggest outcomes from competing risk analysis; § Ha from CHA Bundang Medical Center, CHA University; / from unadjusted cohort at the time of CVR.

Table S7. Reimbursement policies for antiviral therapies.

Nation	Reimbursement Polish for NUC (ETV/TDF)	Year of Commencement of Insurance Benefits for NUC	
		ETV	TDF
	2005-12-14 HBeAg(±) : HBV-DNA 10^5 copies/mL, AST/ALT > 80 IU		2007-01-01
	HBeAg(+) : HBV-DNA 10^5 copies/mL, AST or ALT > 80 IU		
	2010-10-01 HBeAg(-): HBV-DNA 10^4 copies/mL, AST or ALT > 80 IU		
	Cirrhosis/HCC : HBV-DNA > 10^4 copies/mL, AST or ALT > UNL		
Korea	HBeAg(+) : HBV-DNA 10^5 copies/mL, AST or ALT > 80 IU		
	HBeAg(-) : HBV-DNA 10^4 copies/mL, AST or ALT > 80 IU		2012-12-01
	Compensated cirrhosis: HBV-DNA > 10^4 copies/mL		
	Decompensated cirrhosis/HCC: HBV-DNA(+)		
	HBeAg(+) : HBV-DNA > 20000 IU/mL, AST or ALT > 80 IU		
	HBeAg(-) : HBV-DNA > 2000 IU/mL, AST or ALT > 80IU		

Compensated cirrhosis: HBV-DNA > 2000 IU/mL Decompensated cirrhosis/HCC: HBV-DNA(+)			
Taiwan	2003-10-01	HBeAg(+): 18 months, ALT > 5 × UNL or 2 × UNL < ALT < 5 × UNL + HBV DNA>20000 IU/mL	2008.08.01
	2004-08-01	HBeAg(-) : 18 months, ALT > 2*UNL + HBV DNA > 2000 IU/mL	
	2009-11-01	HBeAg(+) & HBeAg(-) : Extend NUC to 3 years, LC remains lifelong	2011-06-01
	2017-01-01	eAg+: no limitation of treatment duration until eAg loss+1 year consolidation	
	2019-02-01	Curative HCC + HBV DNA > 2000 IU/mL	
Hongkong	2010	According to APASL criteria at that time	2010
	2013-2014	ALT > 58 U/L. Cirrhosis proven by liver fibrosis or Fibroscan results There is often delays (1-2 years) from APASL guideline update and change in reimbursement criteria.	2012 2nd line or with pregnancy indication
		No restriction in reimbursement according to viral and biochemical status	2010
China		(varies from region to region)	2014
	Beijing	HBeAg(+) : HBV-DNA 105 copies/mL, AST or ALT > 2 × ULN HBeAg(-): HBV-DNA 104 copies/mL, AST or ALT > 2 × ULN Cirrhosis/HCC : HBV-DNA positive	2005.12. (Shanghai) 2009. (All over China) 2016
	2005	HBeAg(+): HBV DNA > 10 ⁵ copies/mL, ALT ≥ 2 ULN or G ≥ 2 or S ≥ 2 HBeAg(-) : HBV DNA > 10 ⁴ copies/mL, ALT ≥ 2 ULN or G ≥ 2 or S ≥ 2	
	2010	HBeAg(+): HBV DNA > 10 ⁵ copies/mL or 20,000 IU/mL, ALT ≥ 2ULN or G ≥ 2 or S ≥ 2 HBeAg(-): HBV DNA > 10 ⁴ copies/mL or 2000 IU/mL, ALT ≥ 2 ULN or G ≥ 2 or S ≥ 2	
	2015	HBeAg(+): HBV DNA > 20,000 IU/mL, ALT ≥ 2 ULN or G ≥ 2 or S ≥ 2 HBeAg(-): HBV DNA > 2000 IU/mL, ALT ≥ 2 ULN or G ≥ 2 or S ≥ 2	
Guangdong	2019	HBeAg(+): HBV DNA detectable, ALT ≥ 1 ULN or G ≥ 2 or S ≥ 2 HBeAg(-): HBV DNA detectable, ALT ≥ 1 ULN or G ≥ 2 or S ≥ 2	

Listed are the reimbursement policies for ETV and TDF in countries in the included articles. ETV: entecavir; TDF: Tenofovir disoproxil fumarate.