

Tenofovir vs Entecavir on Post-Operative Recurrence-Free and Overall Survival of Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma

Jonggi Choi¹, Chanyoung Jo², Young-Suk Lim¹

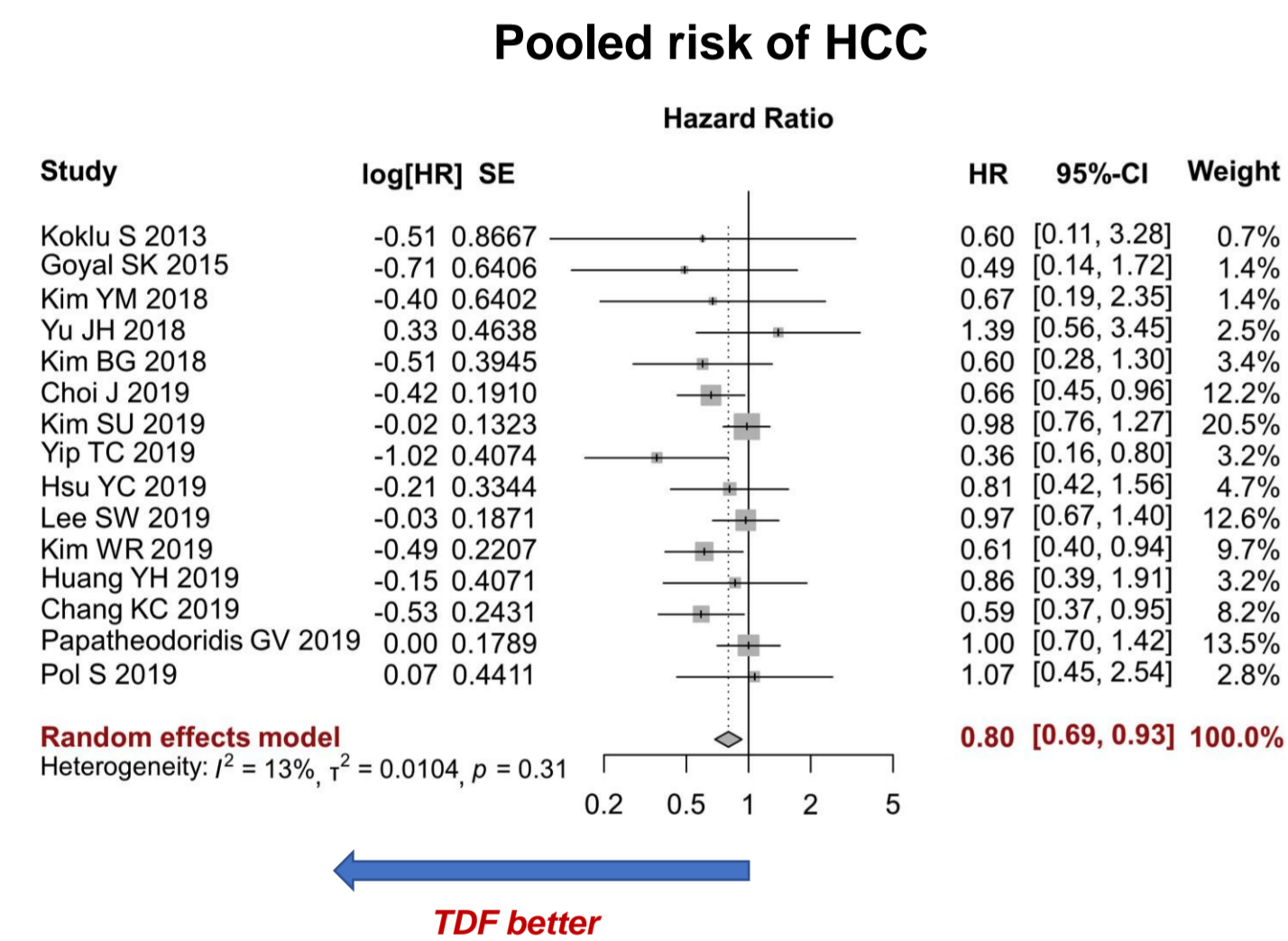
¹Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

²Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea



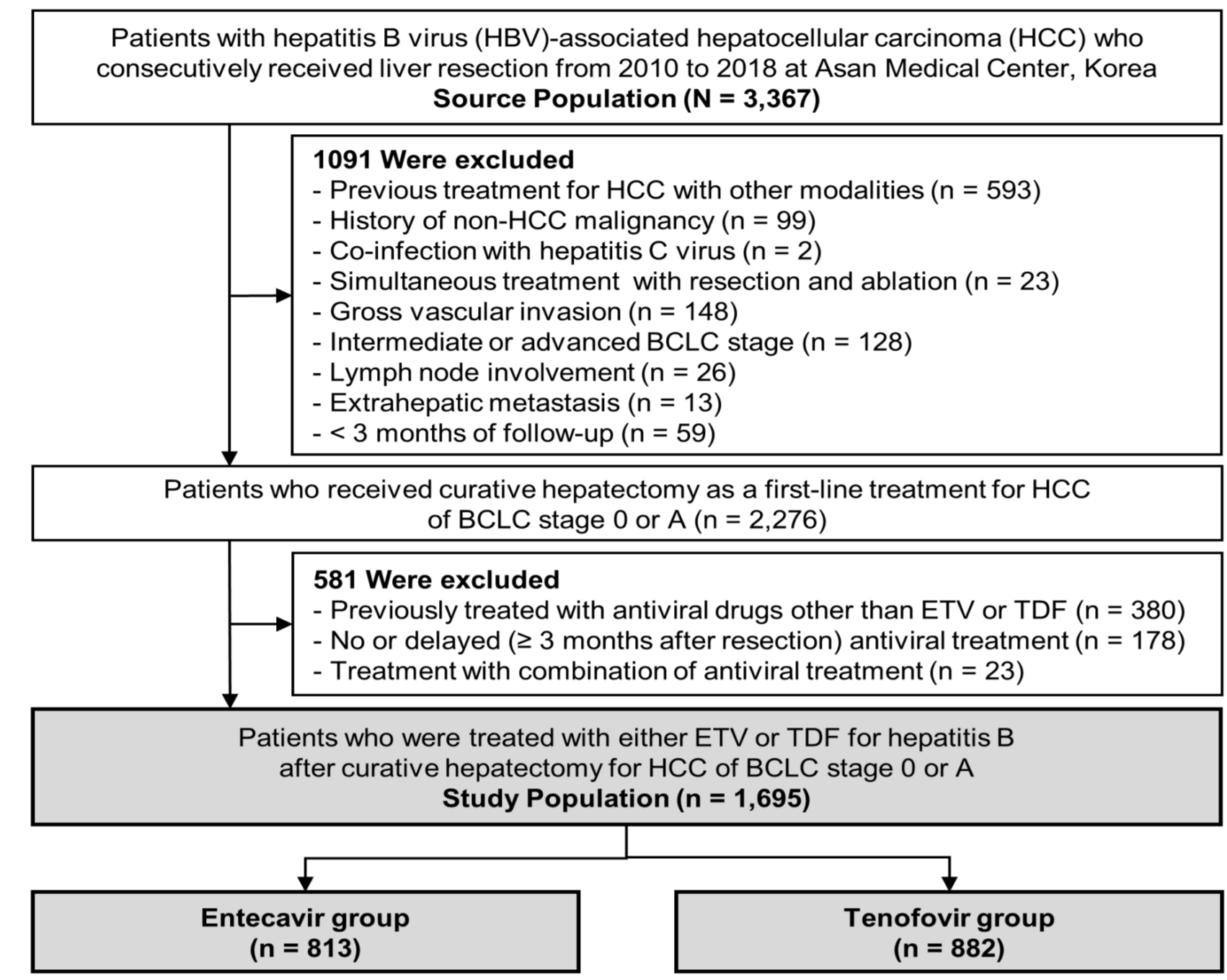
INTRODUCTION

- Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are equally recommended as first-line nucleos(t)ide analogues (NUCs) for chronic hepatitis B (CHB) in clinical practice guidelines
- Although results are still controversial, recent reports that CHB patients with TDF was associated with a lower risk of hepatocellular carcinoma (HCC) development compared to ETV



RESULTS

Study flow



Baseline characteristics

Characteristics	Entire cohort (n = 1,695)		P Value	Propensity score-matched cohort (567 pairs)		SMD
	Entecavir (n = 813)	Tenofovir (n = 882)		Entecavir (n = 567)	Tenofovir (n = 567)	
Demographic characteristics						
Age, years	55.0 ± 8.7	54.6 ± 9.1	0.30	54.6 ± 8.6	54.7 ± 8.3	0.02
Male sex, n (%)	623 (76.6)	671 (76.1)	0.83	430 (75.8)	433 (76.4)	0.01
Diabetes mellitus, n (%)	122 (15.0)	133 (15.1)	0.99	86 (15.2)	88 (15.5)	0.01
Hypertension, n (%)	248 (30.5)	240 (27.2)	0.15	155 (27.3)	171 (30.2)	0.06
Laboratory findings						
HBeAg-positive, n (%)	189 (23.2)	248 (28.1)	0.03	137 (24.2)	149 (26.3)	0.05
HBV DNA, log ₁₀ IU/mL	1.7 ± 2.2	2.8 ± 2.4	< 0.001	2.2 ± 2.3	2.3 ± 2.4	0.03
HBV DNA			< 0.001			0.01
Undetectable	448 (55.1)	263 (29.8)		238 (42.0)	236 (41.6)	
DNA < 2,000 IU/mL	168 (20.7)	271 (30.7)		151 (26.6)	150 (26.5)	
DNA ≥ 2,000 IU/mL	197 (24.2)	346 (39.5)		178 (31.4)	181 (31.9)	
Platelets*, ×1000/mm ³	149 [120-181]	160 [128-198]	< 0.001	153 [125-187]	158 [126-194]	0.06
AST*, IU/mL	29 [23-37]	32 [26-42]	< 0.001	30 [24-40]	31 [25-39]	0.06
ALT*, IU/mL	28 [20-41]	33 [24-46]	< 0.001	31 [21-43]	31 [22-42]	0.04
Albumin*, g/dL	3.8 [3.6-4.1]	3.8 [3.6-4.0]	0.009	3.8 [3.6-4.0]	3.8 [3.6-4.0]	0.01
Total bilirubin*, mg/dL	0.6 [0.5-0.9]	0.6 [0.4-0.8]	< 0.001	0.6 [0.4-0.8]	0.6 [0.4-0.8]	0.05
PT*, INR	1.0 [1.0-1.1]	1.1 [1.0-1.1]	< 0.001	1.0 [1.0-1.1]	1.0 [1.0-1.1]	0.04
AFP*, ng/mL	16.6 [3.8-147.5]	15.8 [4.5-173.7]	0.26	16.2 [4.0-132.9]	15.7 [4.4-162.6]	0.04
AFP			0.71			
AFP < 20 ng/mL	424 (52.2)	469 (53.2)		297 (52.4)	296 (52.2)	0.01
AFP ≥ 20 ng/mL	389 (47.8)	413 (46.8)		270 (47.6)	271 (47.8)	
Pathologic findings						
BCLC stage						
Very early (0)	224 (27.6)	202 (22.9)	0.03	151 (26.6)	142 (25.0)	0.04
Early (A)	589 (72.4)	680 (77.1)		416 (73.4)	425 (75.0)	
Single tumor, n (%)	773 (95.1)	837 (94.9)	0.96	545 (96.1%)	540 (95.2%)	0.02
HCC Size*, cm	2.7 [2.0-3.8]	2.8 [2.0-4.3]	0.01	2.7 [2.0-4.0]	2.8 [2.0-4.1]	0.06
ES grade, worst, n (%)						
I	11 (1.4)	8 (0.9)	0.45	7 (1.2)	7 (1.2)	
II	212 (26.1)	215 (24.4)		154 (27.2)	139 (24.5)	
III	423 (52.0)	454 (51.5)		281 (49.6)	294 (51.9)	
IV	167 (20.5)	205 (23.2)		125 (22.0)	127 (22.4)	
ES grade, background, n (%)						
I	31 (3.8)	22 (2.5)	0.17	21 (3.7)	13 (2.3)	
II	504 (62.0)	542 (61.5)		353 (62.3)	350 (61.5)	
III	272 (33.5)	304 (34.5)		190 (33.5)	186 (32.8)	
IV	6 (0.7)	14 (1.6)		3 (0.5)	8 (1.4)	
Microvascular invasion, n (%)	207 (25.5)	286 (32.4)	0.002	157 (27.7)	148 (26.1)	0.04
Capsular invasion, n (%)	73 (9.0)	79 (9.0)	0.99	49 (8.6)	45 (7.9)	0.03
Satellite nodule, n (%)	34 (4.2)	29 (3.3)	0.40	22 (3.9)	22 (3.9)	0.001
Cirrhosis, n (%)	519 (63.8)	477 (54.1)	< 0.001	340 (60.0)	333 (58.7)	0.03
Follow-up period*, years	4.4 [2.1-6.5]	2.6 [1.5-3.8]	< 0.001	4.4 [2.1-4.3]	3.6 [1.4-4.0]	0.53

AIM

- This study aimed to compare the recurrence of HCC after curative hepatectomy in patients with HBV-related HCC who were treated with either ETV or TDF

METHOD

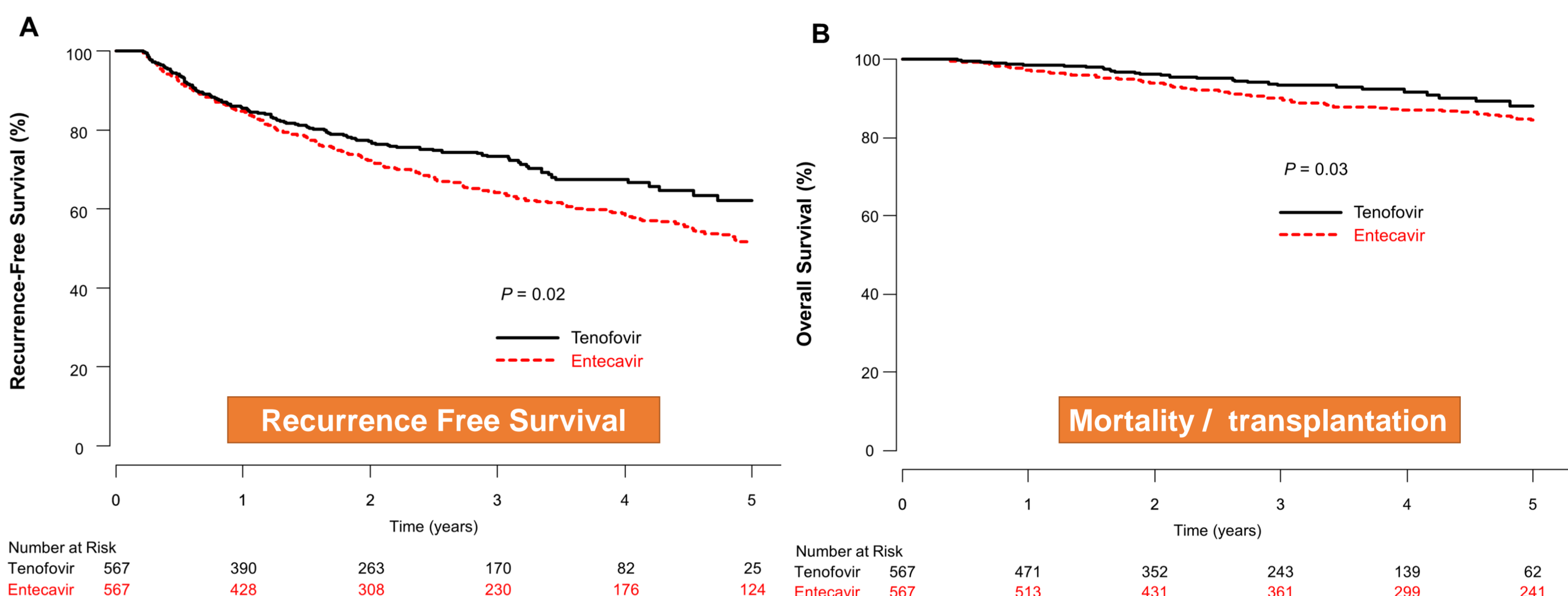
- Historical cohort study of 1,695 consecutive patients in Korea between 2010 and 2018
 - HBV-related HCC
 - Treated with ETV (n=813) or TDF (n=882)
 - BCLC stage 0 or A
 - Received curative hepatectomy

- Primary outcome**
 - HCC recurrence
- Secondary outcome**
 - All-cause mortality or liver transplantation
- Analyzed using propensity-score matching and multivariable Cox model

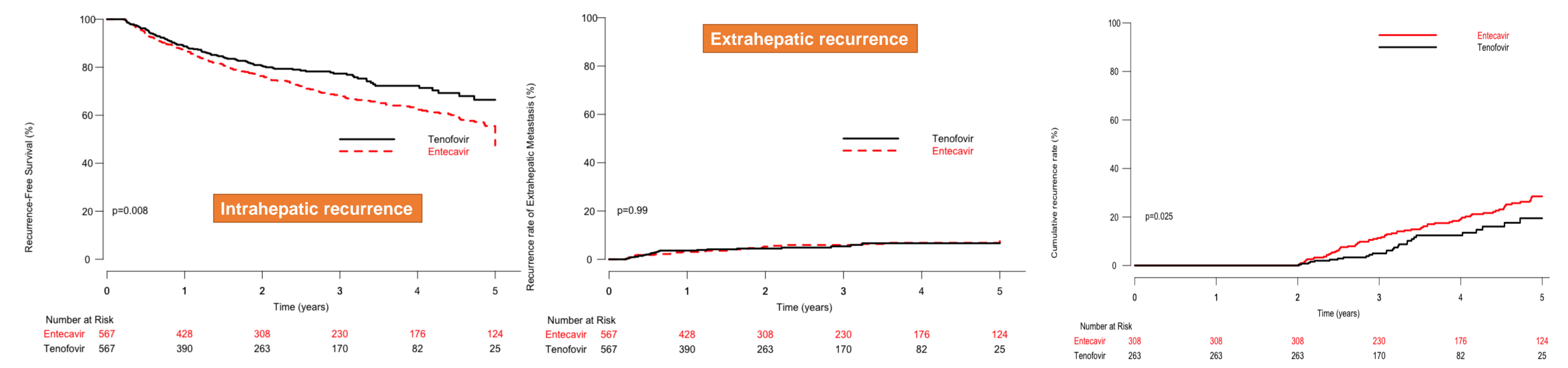
CONCLUSIONS

- TDF treatment was associated with significantly lower rate of HCC recurrence and better overall patient survival than ETV therapy among patients who underwent curative hepatectomy for HBV-related HCC.
- Given the high rate of post-operative recurrence of hepatitis B virus-related HCC and poor prognosis of the patients who developed HCC recurrence, our findings may have considerable clinical implications in the prevention of the cancer recurrence in the patients

Overall outcomes (by propensity score-matching analysis)



Risk of recurrence according to patterns of recurrence



Multivariable Cox model for factors related to recurrence and death/transplantation

Variables	HCC Recurrence			Death or transplantation		
	AHR	95% CI	P value	AHR	95% CI	P value
Antiviral treatment						
Entecavir	1	Reference		1	Reference	
TDF	0.82	0.68-0.98	0.03	0.62	0.44-0.88	0.01
Age, per 1-year increase	1.01	1.00-1.02	0.01			
Male sex	1.70	1.36-2.13	< 0.001	1.67	1.10-2.56	0.02
HBeAg positivity	1.46	1.21-1.76	< 0.001	1.54	1.10-2.15	0.01
BCLC stage						
Very early	1	Reference				
Early	1.20	0.95-1.53	0.13			
Hypertension				1.31	0.95-1.83	0.10
Cirrhosis	1.21	1.01-1.45	0.04	1.52	1.07-2.15	0.02
Size, per 1 cm increase	1.09	1.06-1.13	< 0.001	1.12	1.07-1.17	< 0.001
Microvascular invasion	1.65	1.37-2.00	< 0.001	2.22	1.56-3.15	< 0.001
Capsular invasion	1.43	1.11-1.86	0.006	1.81	1.20-2.72	0.004
Satellite nodule, present	2.10	1.50-2.92	< 0.001	2.44	1.51-3.93	< 0.001
Albumin, per 1 g/dL increase	0.86	0.67-1.10	0.23			
HBV DNA						
Undetectable	1	Reference		1	Reference	
DNA < 2,000 IU/mL	1.03	0.82-1.30	0.79	1.49	0.98-2.29	0.06
DNA ≥ 2,000 IU/mL	1.11	0.89-1.40	0.33	1.11	0.73-1.67	0.63
AST > 40 IU/L	1.36	1.11-1.66	0.003			
AFP ≥ 20 ng/mL	1.06	0.89-1.26	0.54			

Multivariable Cox model for factors related to early and late recurrence

Variables	Early recurrence (< 2 years)			Late recurrence (≥ 2 years)		
	AHR	95% CI	P value	AHR	95% CI	P value
Antiviral treatment						
Entecavir	1	Reference		1	Reference	
TDF	0.79	0.64-0.97	0.03	0.68	0.47-0.97	0.03
Age, per 1-year increase				1.02	1.00-1.04	0.04
Male sex	1.33	1.02-1.75	0.04	1.42	0.97-2.10	0.12
HBeAg positivity	1.20	0.96-1.49	0.11			
BCLC stage						
0 (Very early)	1	Reference		1	Reference	
A (Early)	1.39	1.03-1.84	0.03	1.39	0.95-2.02	0.11
Cirrhosis	1.42	1.14-1.77	0.002	1.27	0.91-1.79	0.16
Size, per 1 cm increase	1.10	1.06-1.13	< 0.001			
Microvascular invasion	1.66	1.34-2.06	< 0.001	1.32	0.91-1.90	0.14
Capsular invasion	1.37	1.01-1.84	0.04	1.86	1.12-3.09	0.02
Satellite nodule, present	1.69	1.19-2.40	0.003			
Total bilirubin, per 1 mg/dL increase	1.38	1.04-1.84	0.03			
HBV DNA						
Undetectable	1	Reference		1	Reference	
DNA < 2,000 IU/mL	0.98	0.74-1.29	0.87	1.03	0.69-1.57	0.86
DNA ≥ 2,000 IU/mL	1.35	1.04-1.76	0.02	1.01	0.69-1.52	0.92
AST > 40 IU/L	1.14	0.89-1.45	0.31	1.64	1.13-2.38	0.01
AFP ≥ 20 ng/mL	1.23	1.00-1.51	0.05	0.87	0.63-1.19	0.38

CONTACT INFORMATION

Young-Suk Lim, MD, PhD
Professor, Department of Gastroenterology
Asan Medical Center, University of Ulsan College of Medicine
88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea
Tel.: +82-02-3010-5933; Fax: +82-02-485-5782
E-mail: limys@amc.seoul.kr