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Association of Prophylactic Anti–Hepatitis B Virus Therapy With Improved Long-term Survival in Patients With Hepatocellular Carcinoma Undergoing Transarterial Therapy

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Background. The effect of prophylactic antiviral therapy (AVT) on survival of patients with hepatitis B virus (HBV)–related hepatocellular carcinoma (HCC) remains unknown. This study aimed to determine whether prophylactic AVT could improve long-term survival in patients undergoing transarterial chemotherapy (TAC).

Methods. Between 2002 and 2016, 2860 newly diagnosed HBV-related patients with HCC treated with TAC were screened to analyze 2 groups based on prophylactic use of antivirals. Treatment effects were analyzed using propensity score (PS) matching (1:1) separately for the entire cohort and each subgroup. The primary endpoint was overall survival.

Results. A total of 1547 patients met the inclusion criteria and 1084 were PS matched for the 2 groups. Median follow-up duration was 16.55 months. In the entire unmatched cohort, patients receiving prophylactic AVT survived significantly longer than those who did not. Among AVT-untreated patients, baseline high viremia and HBV reactivation during treatment were significantly associated with shorter survival. Regarding types of antivirals, survival was significantly longer for patients receiving high-potency antivirals than those receiving low-potency antivirals. Survival differed with antiviral response. In the PS-matched cohort, the prophylactic AVT group survived significantly longer than the nonprophylactic group, irrespective of viral status or tumor stage. Prophylactic AVT remained an independent factor for survival. The association of prophylactic AVT with decreased risk of mortality persisted in patient subgroups after adjusting for baseline risk factors. Sensitivity analyses also confirmed estimated treatment effects.

Conclusions. Prophylactic AVT is associated with significantly improved long-term survival among patients undergoing TAC. High-potency antivirals are indicated for this approach.

Keywords. hepatitis B virus; intra-arterial therapy; reactivation; hepatocellular carcinoma; antiviral therapy.

Transarterial chemotherapy (TAC) with or without embolization is the current mainstay of care for patients with unresectable hepatocellular carcinoma (HCC). Despite its marked direct antitumor effects, TAC can cause toxic or ischemic injury, leading to hepatic decompensation. Furthermore, TAC can reactivate replication of hepatitis B virus (HBV), which can result in disruption or premature termination of planned treatment sessions [1, 2]. Given that HCC often arises with a cirrhotic background, augmented HBV replication together with TAC-induced liver damage can exert additive adverse effects on the liver microenvironment, thereby facilitating tumor progression [3].

Higher levels of HBV DNA are associated with an increased risk of HCC development [4] and cancer recurrence after curative treatment [5]. Pre-TAC high viremia has been suggested to predict a high likelihood of post-TAC recurrence and worse prognosis in antiviral-untreated patients [3, 6]. In addition, a multitude of studies have shown extensive clinical evidence of HBV reactivation and reactivation-induced hepatic exacerbation in patients who undergo TAC [1, 7, 8]. We have previously demonstrated that preemptive lamivudine can significantly decrease the risk of HBV reactivation and facilitate planned sessions of TAC without premature interruption [2, 9]. Given these findings, one may assume that effective suppression of HBV with antiviral therapy (AVT) can be beneficial for overall survival of individuals receiving TAC. However, unlike plenty of data on hepatectomy or radiofrequency ablation [10, 11], clinical data on the role of AVT in patient survival after TAC are extremely limited. Currently, there is no consensus on the optimal timing or type of AVT for patients treated with TAC. Most important, no study so far has attempted to evaluate the effect of prophylactic AVT in conjunction with HBV reactivation on

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long-term survival of TAC-treated patients. Such open questions require long-term follow-up evaluation with a sufficient number of events to be accurately answered.

To address these issues, we conducted a long-term, large-scale cohort study with the objective of determining whether prophylactic AVT might be associated with better survival in patients undergoing TAC with follow-up for more than 10 years. We also analyzed the impact of HBV reactivation or viremic status on patient survival.

METHODS

Patients

The present work was a longitudinal cohort study of prophylactic use of antivirals during TAC. Between January 2002 and December 2016, consecutive patients with newly diagnosed inoperable HBV-associated HCC who received TAC as first-line therapy at our liver unit of The Catholic University of Korea were eligible for enrollment. Patients were excluded if they met any of the following criteria: initial treatment options other than TAC, continued antiviral use before HCC diagnosis, coexisting serious medical disease including other malignancy, serious alcoholic consumption (consumption >20 g/day), autoimmune disease requiring prolonged immunosuppressants, positive test for antibodies to hepatitis C or human immunodeficiency virus, or evidence of hepatic-decompensated complications including encephalopathy, ascites, peritonitis, or hepatorenal syndrome.

Transarterial Treatment

Transarterial chemotherapy of inoperable HCC was performed based on tumor stage and liver function according to the Korean National Cancer Center (KNCC) practice guideline [12]. Briefly, intra-arterial chemoembolization using 50 mg doxorubicin was offered to patients who had multifocal HCCs smaller than 10 cm at 1- to 2-monthly intervals, chemo-lipiodolization of a combination of 50 mg epirubicin and 60 mg cisplatin to patients with HCCs larger than 10 cm and/or peripheral portal vein thrombosis (PVT), and hepatic arterial infusion chemotherapy with high-dose cisplatin and 5-fluorouracil to patients with lobar/main PVT [13, 14]. These transarterial therapies were repeated until radiological disappearance or complete necrosis of viable tumors.

Endpoints and Definitions

The primary endpoint was overall survival. Hepatitis B virus reactivation was defined as a greater than 10-fold increase in serum HBV DNA compared with its baseline level [2]. The diagnosis of HCC was based on histological evidence, α-fetoprotein (AFP) levels, or typical radiological findings according to the KNCC guideline [12]. Prophylactic AVT was defined as initiation of nucleos(t)ide analog (NUC) before the first TAC until 2 weeks afterward. Deferred AVT (>2 weeks after the first TAC) with or without HBV reactivation was all defined as nonprophylactic AVT. High HBV viremia was defined as positive hepatitis B e antigen (HBeAg) or HBV-DNA levels greater than 2000 IU/mL at baseline, whereas low viremia was defined as negative HBeAg and HBV DNA less than 2000 IU/mL. Virological response (VR) was defined as a maintained undetectable HBV-DNA level during therapy [15]. High-potency NUCs were defined as entecavir (ETV) or tenofovir (TDF), while low-potency NUCs were defined as lamivudine (LAM), telbivudine (LdT), clevudine (CLV), or adefovir (ADV).

AVT and Follow-up

Given that our patients had advanced liver disease, AVT was considered for all participants with detectable viremia but, in practice, was primarily administered according to the Korean national insurance policy, which only covered patients with alanine aminotransferase (ALT) levels greater than 80 IU/L and HBV DNA greater than 20 000 IU/mL until 2010. These cutoff levels were modified to ALT greater than 40 IU/L and HBV DNA greater than 2000 IU/mL in 2011. They were further eased to detectable HBV DNA for patients with HCC in 2015. For patients not meeting the insurance criteria at baseline, AVT was delayed until follow-up ALT/HBV-DNA tests met the strict criteria due to the high cost of antivirals. As first-line NUCs, LAM was available since late 1990s, ETV and CLV since 2007, LdT since 2010, and TDF since 2013 in Korea. Adefovir was approved as a rescue therapy for antiviral resistance until 2014.

All patients were tested at baseline for hepatitis B surface antigen (HBsAg), HBeAg, antibodies to HBsAg/HBeAg (Abbott Laboratories), and HBV DNA (VERSANT 3.0; Bayer HealthCare; detection limit >2000 copies/mL until 2007, then real-time polymerase chain reaction–based method with detection limit >34 copies/mL since 2008). Together with HBV tests, AFP and biochemical tests were followed up at baseline and every 1–3 months after starting TAC.

Statistical Analysis

Subjects were divided into 2 cohorts. The prophylactic cohort comprised patients receiving prophylactic AVT, while the nonprophylactic cohort comprised patients who never received AVT or in whom AVT was deferred until HBV reactivation occurred or follow-up ALT/HBV-DNA tests finally met the reimbursement criteria. For patients who initiated AVT, data were analyzed on an intention-to-treat basis.

Analyses were conducted using the Student's *t* test, Mann–Whitney *U* test, chi-square test, and Fisher's exact test, when appropriate. Continuous variables were transformed into 2-level categorical data based on their median values. Survival time was calculated as the time interval from the diagnosis of HCC to death or end of follow-up using Kaplan–Meier's method, and differences were assessed by log-rank test. To examine independent prognostic factors, variables significant on univariate analysis were entered into the multivariate Cox regression

model. Multivariable-stratified analysis of the effect of AVT was performed for different subgroups. Sensitivity analyses were also performed to verify the influence of potential unmeasured confounders on the estimated treatment effect.

We calculated propensity score (PS) using logistic regression to model a dichotomous outcome of the prophylactic or nonprophylactic group and performed a PS matching to balance baseline covariates across groups in the entire cohort as well as in subgroups by baseline viremia and tumor stages. Two-tailed *P* values less than .05 were considered significant. All analyses were performed using SAS software (version 9.3; SAS Institute, Inc).

RESULTS

Study Subjects

Between 2002 and 2016, a total of 2860 patients with newly diagnosed HBV-associated HCC who had baseline and follow-up HBV tests were screened for study enrollment. Among them, 1990 patients underwent TAC as the first treatment for HCC. After excluding patients who received further nontransarterial treatments within 2 years of the first TAC or had continued AVT before HCC diagnosis, we analyzed the remaining 1547 study subjects treated with TAC (Figure 1). Since comparison of antiviral-treated and untreated arms is subject to possible confounding due to differences in baseline characteristics, we performed PS matching to generate 1:1 pairs of patients, one from the prophylactic group and one from the nonprophylactic group. In addition to the entire 1084 PS-matched group, we also used a PS-matching process separately for all subgroups stratified by Barcelona Clinic Liver Cancer (BCLC) stages and HBV viremia groups. These pairs showed no significant differences in clinical data either at baseline between the 2 groups (Supplementary Tables 1 and 2).

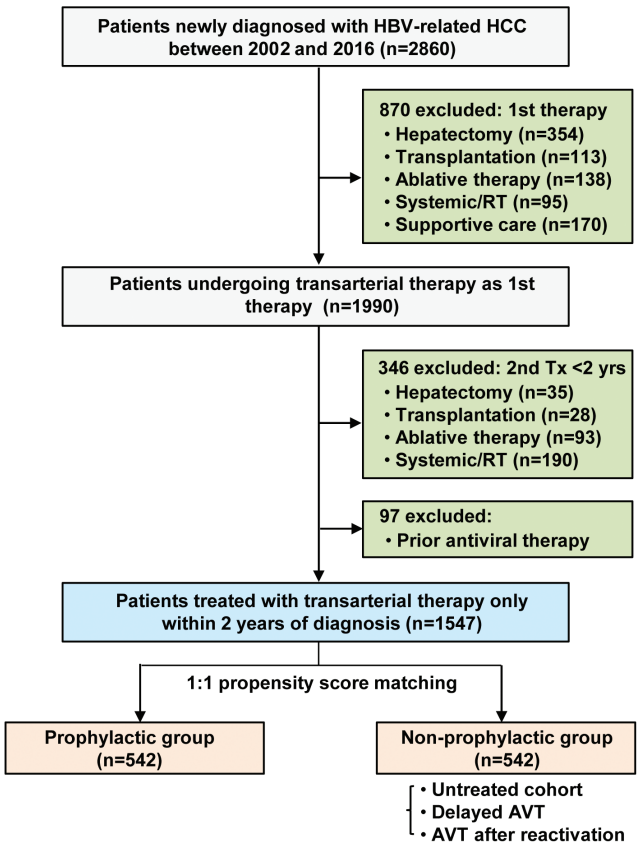


Figure 1. Flow diagram of patient enrollment. Abbreviations: AVT, antiviral therapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; RT, radiotherapy; Tx, treatment.

Baseline characteristics before and after PS matching of study subjects are shown in Table 1. The entire group consisted of 1235 males and 312 females (age interquartile range [IQR], 49–62 years). Overall, we identified 937 patients with AVT and 610 without AVT. With regard to the timing of antiviral initiation, antivirals were initiated prophylactically in 772 patients and deferred in 165 patients (143 with HBV reactivation and 22 without HBV reactivation). Antivirals used included LAM (n = 278), LdT (n = 72), ADV (n = 13), CLV (n = 19), ETV (n = 430), and TDF (n = 125).

Survival in the Entire Group

During a median follow-up of 16.55 months (IQR, 4.97–46.67 months), 750 patients died. The overall 5- and 10-year survival rates of the entire cohort of patients were 29.1% and 19.3%, respectively. Among 675 patients eligible for analysis, major causes of deaths included HCC progression (n = 358, 53.0%) and liver functional deterioration (n = 226, 33.5%). Overall, 81 and 70 patients successfully received hepatectomy and liver transplantation after 2 years of TAC.

For the 610 antiviral-untreated patients, the 1-, 2-, and 3-year cumulative rates of HBV reactivation were 28.6%, 37.9%, and 44.2%, respectively (Supplementary Figure 1). Baseline high viremia and HBV reactivation occurring after TAC were associated with significantly shorter overall survival (Figure 2A and B). For the prophylactic AVT cohort (n = 772), patients receiving high-potency NUCs survived significantly longer than those receiving low-potency NUCs in the subgroup analyses of all NUCs and NUC monotherapy (Figure 2C and D).

Since our study primarily focused on the effect of prophylactic AVT, all subjects were analyzed for 2 groups (prophylactic versus nonprophylactic approach) for further analyses. In the entire unmatched group (n = 1547), the Kaplan–Meier survival curve demonstrated significantly longer overall survival in the prophylactic group than in the nonprophylactic group, with 10-year survival rates of 27.3% versus 12.1%, respectively ($P < .0001$) (Figure 2E).

Survival in the Propensity Score–Matched Group

In the PS-matched group (n = 1084), patients receiving prophylactic NUCs had significantly better overall survival than those who did not, with 10-year survival rates of 26.5% and 12.8%, respectively ($P < .0001$) (Figure 2F).

Table 1. Baseline Characteristics of All Patients Undergoing Transarterial Therapy

	Entire Cohort (N = 1547)			Propensity Score–Matched cohort (n = 1084)			
	Nonprophylaxis (n = 775)	Prophylaxis (n = 772)	*P*	Nonprophylaxis (n = 542)	Prophylaxis (n = 542)	*P*	Standardized Difference, %
Sex			.025			.824	
Male	601 (77.5)	634 (82.1)		427 (78.8)	424 (78.2)		1.3
Female	174 (22.5)	138 (17.9)		115 (21.2)	118 (21.8)		1.3
Age, years	56.3 ± 10.7	55.4 ± 9.2	.068	55.4 ± 10.5	55.6 ± 9.2	.727	2.1
HBV activity			<.001			.604	
Low viremia	407 (52.5)	174 (22.5)		181 (33.4)	173 (31.9)		3.1
High viremia	368 (47.5)	598 (77.5)		361 (66.6)	369 (68.1)		3.1
AST, U/L	55.0 (36–90)	62.0 (40–101)	.001	55.0 (39–91)	60.0 (39–95)	.325	4.0
ALT, U/L	38.0 (26–59)	46.0 (32–73)	<.001	39.0 (28–63)	43.0 (30–66)	.207	3.5
TB, mg/dL	0.9 (0.7–1.5)	1.0 (0.7–1.5)	.602	0.9 (0.7–1.5)	1.0 (0.7–1.5)	.627	0.9
Albumin, g/dL	3.6 ± 0.6	3.6 ± 0.6	.396	3.6 ± 0.6	3.5 ± 0.6	.583	3.3
PT, INR	1.2 ± 0.2	1.2 ± 0.2	.015	1.2 ± 0.3	1.2 ± 0.2	.849	1.2
Child-Pugh score	6.1 ± 1.5	6.0 ± 1.4	.416	6.0 ± 1.4	6.0 ± 1.4	.862	1.1
Child-Pugh class			.470			.845	
A	579 (74.7)	589 (76.3)		409 (75.5)	401 (74.0)		3.4
B	174 (22.5)	168 (21.8)		120 (22.1)	128 (23.6)		3.5
C	22 (2.8)	15 (1.9)		13 (2.4)	13 (2.4)		0.0
Tumor size, cm	7.2 ± 5.1	6.3 ± 5.0	<.001	6.5 ± 4.8	6.8 ± 5.2	.361	5.8
Tumor number			.972			.576	
Single	341 (44.0)	339 (43.9)		231 (42.6)	240 (44.3)		3.4
Multiple	434 (56.0)	433 (56.1)		311 (57.4)	302 (55.7)		3.4
Portal vein invasion			.019			.347	
Present	289 (37.3)	244 (31.6)		179 (33.0)	193 (35.6)		5.4
Absent	486 (62.7)	528 (68.4)		363 (67.0)	349 (64.4)		5.4
Distant metastasis			.150			.660	
Present	131 (16.9)	110 (14.2)		79 (14.6)	74 (13.7)		2.6
Absent	644 (83.1)	662 (85.8)		463 (85.4)	468 (86.3)		2.6
α-Fetoprotein, ng/mL	139.5 (12–1584)	98.9 (11–1281)	.323	111.5 (11–1020)	123.5 (10–1613)	.784	1.6
BCLC stage			.078			.990	
0	34 (4.4)	34 (4.4)		24 (4.4)	24 (4.4)		0.0
A	167 (21.5)	205 (26.6)		138 (25.5)	132 (24.4)		2.6
B	228 (29.4)	235 (30.4)		160 (29.5)	158 (29.2)		0.8
C	320 (41.3)	281 (36.4)		206 (38.0)	213 (39.3)		2.7
D	26 (3.4)	17 (2.2)		14 (2.6)	15 (2.8)		1.1
Transarterial therapy			.027			.792	
TAC-doxo	436 (56.3)	486 (63.0)		325 (60.0)	314 (57.9)		4.2
TAC-EC	252 (32.5)	213 (27.6)		163 (30.1)	172 (31.7)		3.4
HAIC–intra-arterial	87 (11.2)	73 (9.5)		54 (10.0)	56 (10.3)		0.9

Data are expressed as mean ± SD or median (interquartile range). Data are presented as no. (%) for categorical variables unless otherwise indicated.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; doxo, doxorubicin; EC, epirubucin and cisplatin; HAIC, hepatic artery infusion chemotherapy; HBV, hepatitis B virus; INR, international normalized ratio; PT, prothrombin time; TAC, transarterial chemotherapy; TB, tuberculosis.

In addition, PS-matched analyses were separately done for each subgroup of interest stratified by baseline viremia status and tumor stages (Supplementary Tables 1 and 2). As a result, prophylactic AVT again showed significantly better survival than the nonprophylactic group in PS-matched subgroups, irrespective of baseline viremia status and in patients with BCLC-A and BCLC-B HCC. For BCLC-0 and BCLC-C HCC, a modest therapeutic effect with a borderline trend was seen, probably due to a small number of cases analyzed and baseline disease advancement, respectively (Figure 3).

Survival According to Virological Response

After excluding patients with delayed AVT initiation or early death/loss to follow-up (<3 months), 705 patients were evaluable for assessment of VR. Overall, 412 (58.4%) with prophylactic AVT achieved VR, while 293 (41.6%) did not, mostly due to drug resistance. Survival differed with antiviral response. Patients achieving VR had significantly longer survival than nonresponders or AVT-untreated patients (Figure 4A and B). The survival benefit still existed in AVT-treated patients without VR compared with AVT-untreated patients among the high-viremia group (Figure 4B).

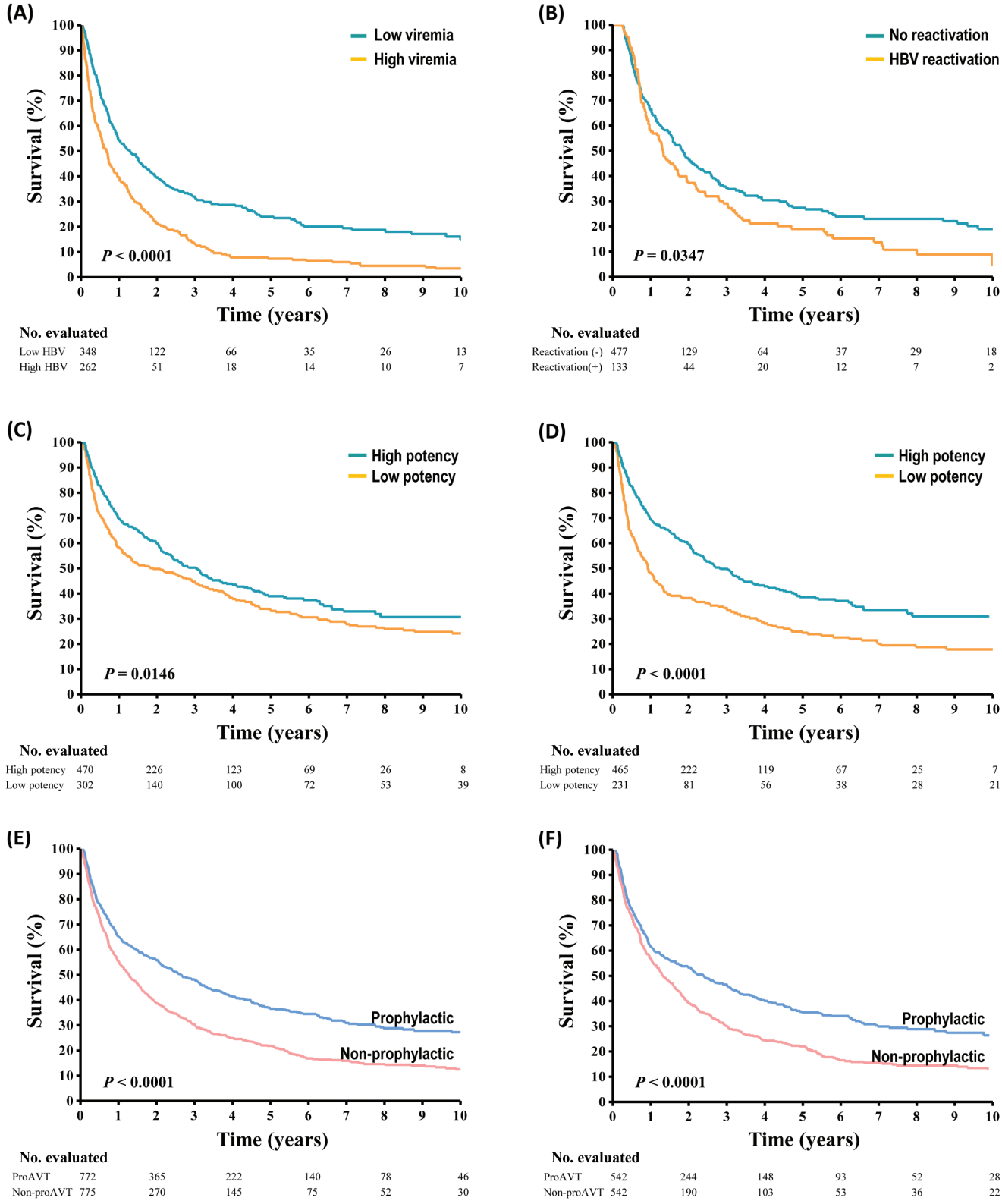


Figure 2. Overall survival of patients undergoing transarterial chemotherapy based on viremia status (*A*) and HBV reactivation (*B*) in antiviral-untreated patients. Overall survival of patients receiving all kinds of antivirals (*C*) and antiviral monotherapy (*D*). Significantly longer survival was seen in the prophylactic group than in the nonprophylactic group in an unmatched cohort (*E*) and a propensity score-matched cohort (*F*). Abbreviations: AVT, antiviral therapy; HBV, hepatitis B virus; Non-pro, nonprophylactic; Pro, prophylactic.

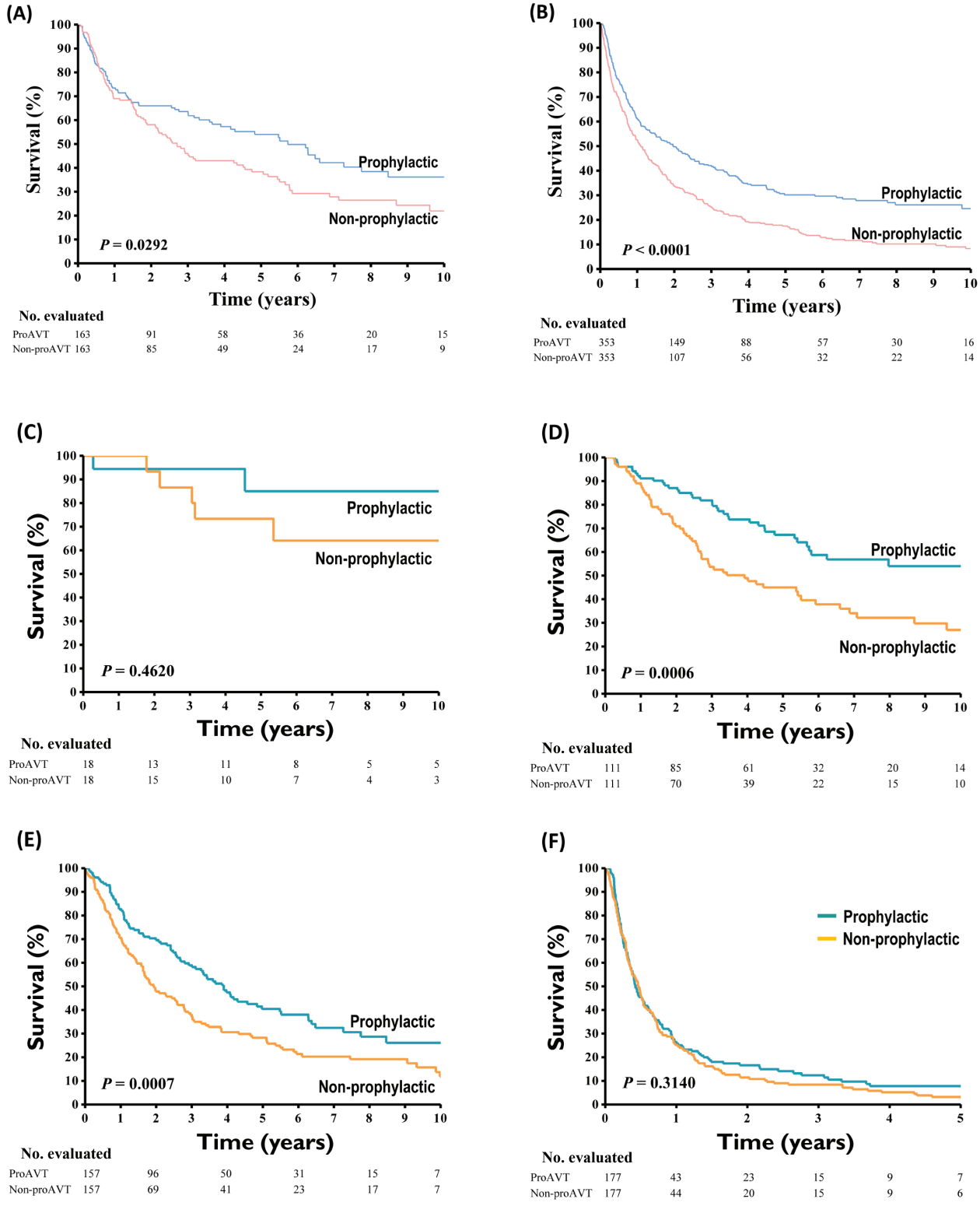
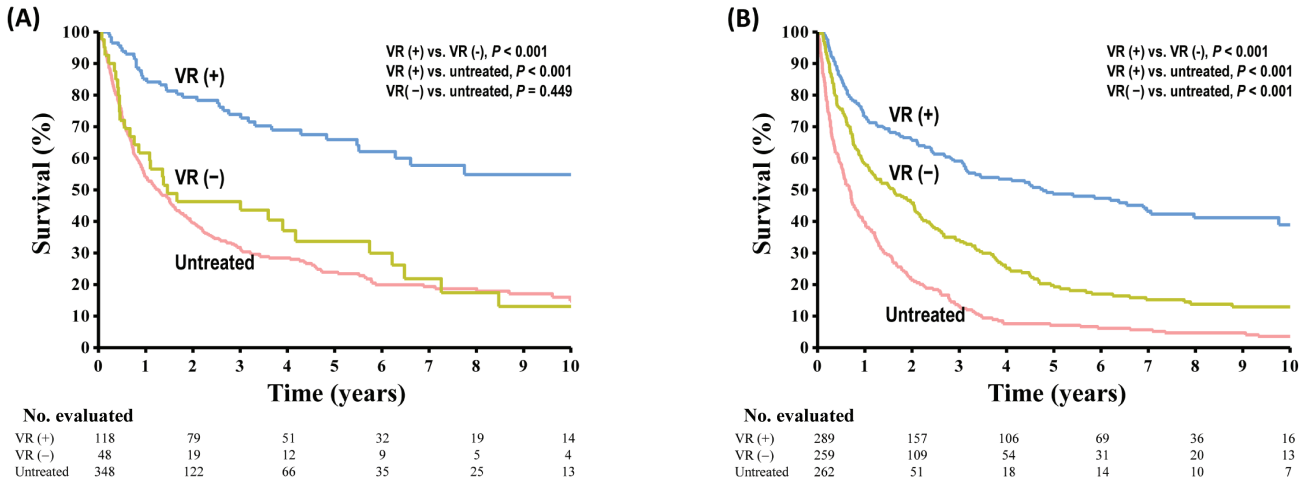


Figure 3. Overall survival of propensity score-matched subgroups based on baseline viremia status (*A*, *B*) and BCLC staging (*C*–*F*). *A*, Low-viremia group; *B*, high-viremia group; *C*, BCLC stage 0; *D*, BCLC stage A; *E*, BCLC stage B; *F*, BCLC stage C. Abbreviations: AVT, antiviral therapy; BCLC, Barcelona Clinic Liver Cancer; Non-pro, nonprophylactic; Pro, prophylactic.

Analysis of Prognostic Factors

Without controlling for other factors, prophylactic AVT was associated with reduced mortality during TAC ($P < .001$). In multivariable regression analysis, prophylactic AVT remained as an independent factor for mortality in patients treated with TAC (hazard ratio [HR], 0.62; 95% confidence interval [CI],



(C)

Subgroup	Untreated	Event Rate(%)	Treatment	Event Rate(%)	HR (95% CI)	*P* value	Interaction *P* value
Age							
≤60 years	287/375	76.5	238/385	61.8	0.70 (0.59-0.81)	<0.001	0.809
>60 years	131/167	78.4	94/157	59.9	0.69 (0.53-0.90)	0.007	
Gender							
Male	335/427	78.5	270/424	63.7	0.72 (0.62-0.83)	<0.001	0.331
Female	83/115	72.2	62/118	52.5	0.61 (0.44-0.83)	0.002	
Child-Pugh class							
A	296/402	73.6	223/398	56.0	0.65 (0.56-0.77)	<0.001	0.423
B+C	122/140	87.1	109/144	75.7	0.79 (0.62-1.00)	0.051	
ALT							
<40 U/L	206/283	72.8	135/251	53.8	0.67 (0.55-0.83)	<0.001	0.836
≥40 U/L	212/259	81.9	197/291	67.7	0.67 (0.55-0.80)	<0.001	
HBV activity							
High viremia	302/361	83.7	247/369	66.9	0.63 (0.48-0.81)	<0.001	0.430
Low viremia	116/181	64.1	85/173	49.1	0.72 (0.61-0.84)	<0.001	
AFP							
≤100 ng/mL	189/265	71.3	125/261	47.9	0.56 (0.45-0.70)	<0.001	0.058
>100 ng/mL	229/277	82.7	207/281	73.7	0.78 (0.66-0.93)	0.005	

Figure 4. Survival of patients according to antiviral response in the low-viremia group (*A*) and high-viremia group (*B*). *C*, Multivariable-stratified analyses of association between prophylactic antiviral therapy and patient survival. Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AVT, antiviral therapy; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; VR, virological response.

0.53–0.72; $P < .001$) (Table 2). Additional prognostic factors included viremia, ALT levels, liver function, AFP, and tumor extent. Prophylactic AVT still remained independently predictive of patient survival, even when analyzed separately according to baseline viremia status (Supplementary Table 3).

Multivariable-stratified Analysis for Antiviral Therapy

As depicted in Figure 4C, multivariable-stratified analyses verified the association of prophylactic therapy with a decreased risk of mortality in nearly all patient subgroups, especially for groups of females (HR, 0.61; 95% CI, 0.44–0.83), those with high viremia (HR, 0.63; 95% CI, 0.48–0.81), and those with lower AFP levels (HR, 0.56; 95% CI, 0.45–0.70). Indeed, we found no statistically significant interactions of prophylactic therapy with age, sex, Child-Pugh class, ALT, viremia status, or AFP levels, indicating that treatment effects were homogeneous (Figure 4C).

Sensitivity Analyses

Sensitivity analyses were performed separately with the type of TAC and study periods, because Korean reimbursement criteria for anti-HBV therapy were modified and treatment options for HCC became more diversified since 2010 in our center. As a

Table 2. Analysis of Baseline Prognostic Factors for Survival

	Univariate *P* Value	Multivariate HR (95% CI)	*P* Value
Prophylactic AVT	<.001	0.62 (.53–.72)	<.001
Male sex	<.001	1.17 (.97–1.42)	.096
Age >55 years	.034	1.06 (.91–1.23)	.411
High viremia	<.001	1.33 (1.12–1.57)	.001
AST >60, U/L	<.001	1.01 (.98–1.03)	.387
ALT >40, U/L	<.001	1.25 (1.08–1.46)	.003
Child-Pugh class B/C	<.001	1.03 (1.02–1.04)	<.001
α-Fetoprotein >100, ng/mL	<.001	1.53 (1.31–1.79)	<.001
Tumor size >5 cm	<.001	1.84 (1.52–2.21)	<.001
Tumor multiplicity	<.001	1.45 (1.24–1.69)	<.001
Portal vein invasion	<.001	1.67 (1.2–2.24)	.001
Metastasis	<.001	1.74 (1.39–2.19)	<.001
BCLC stage C/D	<.001	1.01 (1.00–1.03)	.031

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVT, antiviral therapy; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HR, hazard ratio.

result, the prophylactic approach provided significantly longer survival than nonprophylactic approach among both all unmatched 1872 patients starting with TAC ($P < .001$) and 154 PS-matched patients with BCLC-B HCC undergoing TAC only through the entire study period ($P = .043$) (Figure 5A and B). For both study periods, 2000–2009 (n = 917) and 2010–2016 (n = 630), prophylactic AVT was still associated with significantly longer overall survival than nonprophylactic therapy ($P < .0001$ and $P = .0009$, respectively; Figure 5C and D).

DISCUSSION

This long-term study involving a large cohort clearly demonstrated that prophylactic AVT significantly improved overall survival in patients undergoing TAC. Its positive effects persisted in all subgroups stratified by demographic characteristics, and prophylactic AVT was identified to be an independent factor for survival after TAC. Importantly, our findings confirmed the hypothesis that prophylactic AVT could improve overall patient survival in the setting of TAC. To the best of our knowledge, this is the first study to address the impact of prophylactic AVT in association with HBV reactivation and the type of NUCs on long-term survival in 10 years following TAC-treated patients.

Our analysis of an AVT-untreated cohort raised several clinically relevant points. First, high viremia significantly decreased survival of TAC-treated patients. Second, patients frequently experienced HBV reactivation during TAC. Third, patients experiencing HBV reactivation had worse overall survival than those who did not. Last, if antiviral prophylaxis is considered for untreated patients, high-potency NUC should be administered before TAC, because high-potency drugs could provide better outcomes. The unfavorable outcomes of the patients with unsuppressed HBV load indicate detrimental effects of viremia, supporting the notion of prophylactic AVT with high-potency NUCs in order to improve patient survival. While speculative, adequate control of viral replication is likely to be advantageous not only by preventing reactivated hepatitis B but also by offering additive benefits to form antitumoral microenvironments through counteracting cancer-promoting inflammation by HBV [3, 7].

Currently, there is a lack of solid evidence on the role of AVT in patient survival on TAC. Although 2 studies recently reported patient survival with AVT [16, 17], these studies only introduced small sample sizes with short-term follow-up without information on the effect of viremia/reactivation and the type of NUCs or they only analyzed a limited number of patients with high-level viremia or recurrent HCC. Our study differs from those studies in that we specifically highlighted the adverse effects of viremia or HBV reactivation during TAC and, more importantly, long-term survival benefits of prophylactic AVT, irrespective of baseline characteristics. With the advantage of a large cohort, our detailed analyses endorse prophylactic AVT to be administered for all patients with HBV-related HCC who are to receive TAC, because the prophylactic effects persisted after adjustment for their baseline risk or other confounders. The international practice guidelines lack a distinct specification regarding the need of prophylactic AVT for patients undergoing TAC [15, 18, 19]. In this respect, our study provides new compelling evidence that TAC should be added to the list of indications for prophylactic AVT.

It should be noted that the survival benefits with prophylactic AVT were observed not only in patients with high-level viremia but also in those with low-level viremia. This suggests that even low-level viremia can have a harmful effect on patients with HCC, with either HBV reactivation (44.2% at 3 years) or intermittent episodes of viral increase, which might ultimately compromise overall patient survival. This result coincides with the current finding that high-potency NUCs provided better survival than low-potency NUCs (Figure 2C and D), emphasizing the importance of complete suppression of HBV to the lowest

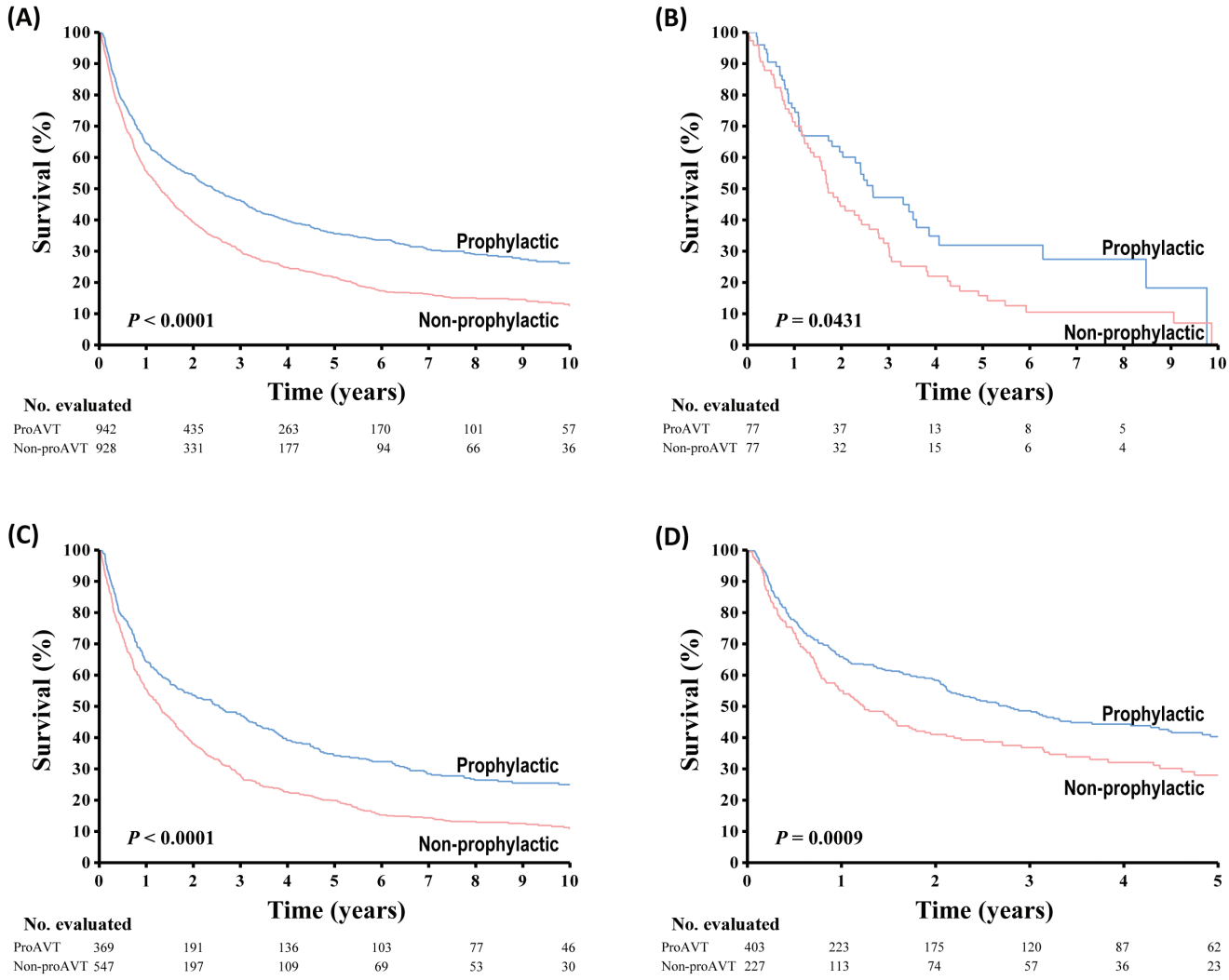


Figure 5. Sensitivity analyses based the type of TAC and the study period. Survival curves of all patients starting with TAC (*A*) and propensity score-matched patients with BCLC-B hepatocellular carcinoma receiving TAC only throughout the study period (*B*). *C* and *D*, Survival based on 2 study periods (*C*: 2000–2009; *D*: 2010–2016). Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; Non-pro, nonprophylactic; Pro, prophylactic; TAC, transarterial chemotherapy.

possible level during treatment. Given the indirect low-quality evidence that recommends AVT to patients with advanced liver disease and low-level viremia [19], our overall findings add accumulating evidence that highly potent AVT is necessary for such settings and for all patients receiving TAC, not just limited to patients with high-viremia or poor baseline risks.

Although the protective effects of AVT appeared to be attenuated in patients with BCLC-0 or BCLC-C, their survival curves show similar patterns as presented in other BCLC stages and a significant survival benefit was observed in patients with BCLC-C HCC and Child-Pugh class A (Supplementary Figure 2). Thus, the attenuated effects indicate the small sample size analyzed (BCLC-0) or baseline disease severity with insufficient survival time for patients to benefit from AVT (BCLC-C), which does not contradict the beneficial role of antivirals. Importantly, our observations of the significant benefits with AVT despite inclusion of many cases of advanced-stage HCC, which might diminish the statistical power of associations, again indicate that patients eligible for TAC should be given prophylactic AVT and its benefits could be much greater than shown herein.

Our study has several limitations. There are many patients with early or advanced tumors who may choose nontransarterial treatments. This reflects global patterns of treatment choice varying with regions/countries [20]. To exclude confounding influences by other treatments, we selected patients undergoing TAC only for at least 2 years after HCC diagnosis. Antiviral therapy was not randomized. However, it would be unethical to involve antiviral-untreated controls in settings of HCC. Rather, the strict AVT reimbursement criteria before 2011 provided us with a unique opportunity to explore the long-term effect of viremia on HCC survival with the inclusion of contemporary

untreated controls. Changing patterns of AVT and TAC modalities over more than 10 years of the study period might have affected outcomes. However, sensitivity analyses with the 2-stage study period and different sets of TAC use also verified the treatment effects. Importantly, gains from prophylactic AVT were still apparent in PS-matched patients undergoing TAC only through the entire study period for BCLC-B HCC, for which TAC is commonly indicated [12]. Last, the nonprophylactic arm was a heterogeneous cohort regarding AVT. However, our study design for the nonprophylactic group was not limited to non-AVT but included deferred AVT, which might have led to an underestimation of the associations. Furthermore, the treatment effects were confirmed using rigorous statistical approaches, which provide convincing evidence and confirm the robustness of our study results.

In conclusion, prophylactic use of high-potency AVT is associated with significantly longer overall survival in patients with HBV-associated HCC undergoing TAC. The current findings provide accumulating evidence of specific recommendations for TAC to be added to the list of indications for prophylactic AVT.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. W. J.: study concept and design; S. H. Y., S. W. L., J. H. K., S. W. N., H. C. N., S. H. Y., P. S. S, S. H. B., J. Y. C., and S. K. Y.: acquisition of data; J. W. J. and J. Y. C.: analysis and interpretation of data; J. W. J.: drafting of the manuscript; S. H. Y. and J. W. J.: statistical analysis; J. W. J. and J. Y. C.: study supervision.

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Potential conflicts of interest. J. W. J. has served as a consultant to or has served on the advisory board of Bristol-Myers Squibb (BMS), Merck Sharp & Dohme, AbbVie, Gilead, Bayer, and Roche. S. H. B. has served as a consultant to Bayer. S. K. Y. has served as a consultant to or has served on the advisory board of BMS, AbbVie, Gilead, and Bayer. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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