Clinical Indication of Aspirin Associated With Reduced Risk of Liver Cancer in Chronic Hepatitis B: A Nationwide Cohort Study

Byungyoon Yun, MD[1], Sang Hoon Ahn, MD, PhD[2,3,4], Jin-Ha Yoon, MD, PhD[1,5,*] and Beom Kyung Kim, MD, PhD[2,3,4,*]

INTRODUCTION: **Despite the overall association of aspirin on reduced hepatocellular carcinoma (HCC) risk, there have been few studies on its benefit according to specific clinical conditions among hepatitis B virus (HBV)-infected patients. This study aimed to identify subgroups which benefit from long-term aspirin use.**

METHODS: **Nationwide data covering the HBV-infected population in the Republic of Korea from 2010 to 2011 were analyzed. Patients who had been taking Aspirin for ≥3 years were classified as aspirin users. The primary outcome was HCC development. The multivariable Fine and Gray competing risk regression model was used to estimate the adjusted hazard ratio (HR) in the entire cohort. Propensity score matching at a 1:4 ratio was also performed.**

RESULTS: **Among 161,673 patients, 7,083 newly developed HCC during follow-up (mean: 7.5 years). After adjusting for age, sex, hypertension, diabetes mellitus, dyslipidemia, cirrhosis, antivirals, metformin, statin, smoking, alcohol consumption, and obesity, aspirin users (n = 9,837) were less likely to develop HCC; the adjusted HR was 0.84 ($P = 0.002$) in the entire cohort and 0.87 ($P = 0.010$) in the matched cohort. Association of aspirin use with all-cause mortality was not significant (HR = 0.93; $P = 0.192$), whereas association with liver-related mortality was significant (HR = 0.79; $P = 0.019$). A significant association was observed in the subgroups with cirrhosis, both sexes, hypertension, non–diabetes mellitus, nonantivirals against chronic hepatitis B, nonmetformin use, nonstatin use, both smoking histories, and obesity (all $P < 0.05$).**

DISCUSSION: **Long-term aspirin use is significantly associated with reduced risk of HCC in chronic HBV patients. More comprehensive studies should be implemented to clarify the causal relationship.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C472, http://links.lww.com/AJG/C473, http://links.lww.com/AJG/C474, http://links.lww.com/AJG/C475, and http://links.lww.com/AJG/C476.

Am J Gastroenterol 2022;117:758–768. https://doi.org/10.14309/ajg.0000000000001725

INTRODUCTION

Chronic hepatitis B virus (HBV) infection has been a major public health problem affecting approximately 300 million people worldwide, especially in HBV-endemic areas such as East Asian countries (1–3). It is one of the crucial causative factors for the development of hepatocellular carcinoma (HCC), which is now the second leading cause of cancer-related mortality (4), and is expected to increase almost twofold by 2040 (5,6). Long-term antiviral therapy (AVT) using potent oral nucleos(t)ide analogs, which can effectively lead to virological and biochemical remission, remarkably reduces the risk of HCC development (7). However, because hepatocarcinogenesis among patients with chronic HBV infection progresses through complex pathways involving viral, host, and environmental factors, it is difficult to completely eliminate the risk of HCC. Therefore, along with effective AVT, other effective strategies of chemoprevention for HCC have recently been reappraised (8).

Recently, several plausible mechanisms have been raised that aspirin may have a protective association on HCC by inhibiting platelet activation pathway (9) and inducing apoptosis of cancer (10). Indeed, patients receiving aspirin reportedly had a significantly favorable clinical outcome in terms of reduced risk of HCC development, with hazard ratios (HRs) ranging from 0.7 to 0.8, in populations with chronic liver diseases, including chronic HBV infection (11–14). Given that HBV is prevalent in East Asian countries, there have been many studies designed to elucidate the

[1]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, South Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; [3]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, South Korea; [4]Yonsei Liver Center, Severance Hospital, Yonsei University Health System, Seoul, South Korea; [5]Department of Occupational Health, Graduate School of Public Health, Yonsei University, Seoul, South Korea. **Correspondence:** Jin-Ha Yoon, MD, PhD. E-mail: flyinyou@yuhs.ac. Beom Kyung Kim, MD, PhD. E-mail: beomkkim@yuhs.ac.
*Jin-Ha Yoon and Beom Kyung Kim equally contributed to this work as cocorresponding authors.
Received December 11, 2021; accepted March 1, 2022; published online March 14, 2022

protective association between aspirin use and HCC incidence in the general population, although few studies have been conducted with an at-risk population of chronic HBV.

Although a well-controlled cohort study from Taiwan reported a protective association of aspirin on HCC in chronic HBV patients, the study did not control for minimal latency of HCC and long-term aspirin use (11). Furthermore, studies with small sample sizes might not be able to determine whether aspirin use has a protective association, even with HBV infection-related comorbidity, including liver cirrhosis. In the same context, more comprehensive analysis is needed to determine the clinical implications in patients with different metabolic health status and other drug use.

Therefore, we aimed to assess the protective association of long-term aspirin on the risk of HCC, with a view to propose a clinical indication for aspirin according to metabolic factors and other drug use.

METHODS

Data source and study population

This nationwide cohort study used data from the National Health Insurance Service (NHIS) of the Republic of Korea between January 1, 2010, and December 31, 2018. This database includes patient demographic data, outpatient visit or hospitalization dates, principal diagnosis codes, medical examination and treatment, detailed statements of drug prescription, and health examination data. The *International Classification of Diseases 10th edition* (*ICD-10*) codes used in this study are summarized in Supplementary Table 1 (http://links.lww.com/AJG/C475).

From this database, all patients with chronic hepatitis B (CHB, with/without hepatitis delta virus [HDV]), aged ≥40 years, and receiving a health examination were screened for potential eligibility. Patients with any records of outpatient visit or hospitalization in 2010 and 2011 were enrolled. Because the report of the World Trade Center Health Program suggested that any study related to solid cancers should include enough time lag for several years (15), an aspirin user was defined as a patient who has been taking aspirin for at least 3 years or more during the follow-up period in this study; this is different from definitions used in other studies (11,13). Prescription time-distribution matching, which randomly matches the index date of nonusers with the index date of aspirin users with replacement, was performed to set the index date of nonusers by controlling immortal time bias (16). The exclusion criteria were as follows: (i) history of HCC; (ii) coinfection with hepatitis C virus or human immunodeficiency virus; (iii) history of extrahepatic malignancy; (iv) history of myocardial infarction or ischemic stroke; (v) decompensated liver cirrhosis; and (vi) patients with HCC, death, or orthotopic liver transplantation (OLT) before an additional 3-year time lag from the index date. All diseases were defined using *ICD-10* codes when 3 or more outpatient visits or 1 or more hospitalizations occurred. The exclusion criteria of decompensated liver cirrhosis, which is summarized in Supplementary Table 2 (see Supplementary Digital Content 4, http://links.lww.com/AJG/C475), were decided based on the *ICD-10* code for diagnosis and claim code for the procedure related to the diagnosis of participants. The detailed schematic flow of the patient selection process is described in Figure 1.

This study was approved by the institutional review board of the Yonsei University Hospital (IRB 4-2018-1132). The need for informed consent was waived because data from the NHIS were not individually identifiable.

Main outcomes

The primary endpoint of our study was HCC occurrence, with death and OLT considered as competing risk events. Liver-related and all-cause mortality was set to secondary endpoints. The date of HCC occurrence was set to the first day of outpatient visit or hospitalization for diagnosis. The last follow-up date was set to the date of HCC occurrence, death, OLT, or the end of the study period (December 31, 2018). The time lag for the outcomes was primarily defined as 3 years from the index date based on the definition of a long-term aspirin user.

Definition of cohort variables

Disease histories of hypertension (HTN), diabetes mellitus (DM), dyslipidemia, and liver cirrhosis were defined using the *ICD-10* codes (see Supplementary Table 1, Supplementary Digital Content 4, http://links.lww.com/AJG/C475). AVT against CHB, metformin use, and statin use was defined using the same criteria as aspirin use, which was set to a prescription of 3 years or more. AVT against CHB included tenofovir, entecavir, lamivudine, adefovir, clevudine, and peginterferon-alpha. Based on smoking history, patients were classified as nonsmokers, ex-smokers, and current smokers. Patients who consumed 5 or more glasses of alcohol per week in women or 7 glasses or more of alcohol per week in men were defined as heavy alcohol drinkers, whereas others were defined as none to social drinkers. Obesity was categorized based on the body mass index of Asian guidelines as follows: underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (≥25 kg/m^2) (17).

Statistical analyses

For continuous and categorical data, independent *t* tests and χ^2 tests were used to examine differences between patients with and without aspirin use, respectively. HRs with 95% confidence intervals (CIs) were calculated using Cox regression analysis, and competing risk of mortality and OLT were controlled by Fine and Gray regression (FGR). Adjusted HRs were calculated with adjustments for age, sex, HTN, DM, dyslipidemia, liver cirrhosis, AVT against CHB, metformin use, statin use, smoking history, alcohol consumption, and obesity in a multivariable survival analysis. The adjusted HRs of liver-related and all-cause mortality were further calculated using the equivalent method of survival analysis. Multicollinearity of the models was measured by using variance inflation values. Moreover, to elucidate the role of aspirin by certain characteristics, the entire cohort was stratified according to HNT, DM, dyslipidemia, liver cirrhosis, AVT against CHB, metformin use, statin use, smoking history, alcohol consumption, and obesity. The same methods were used in each subgroup analysis, and the *P* value for interaction was calculated for each stratum. Interaction analysis between aspirin and statin use on HCC was further conducted.

Several sensitive analyses were performed. To ensure the time lag effect between aspirin and cancer incidence, analysis was performed by excluding patients with outcome or competing risk events within an additional time lag of 6, 12, and 24 months (13). In addition, the proportion of coinfection with HDV was estimated, and adjusted HRs were calculated by additionally adjusting HDV in the FGR model. To elucidate the association of long-term aspirin, adjusted HRs of HCC were estimated by using

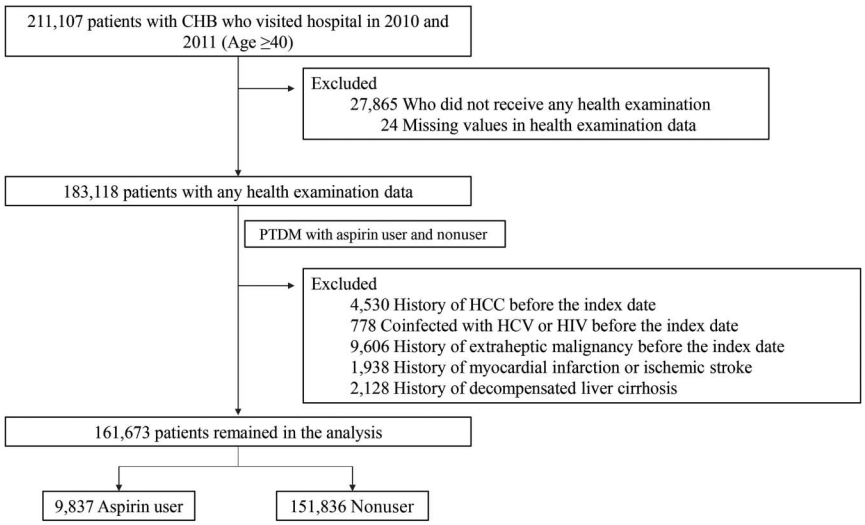

Figure 1. Schematic flow of patient selection. CHB, chronic hepatitis B; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PTDM, post-transplant diabetes mellitus.

definition of aspirin user with the use of aspirin for 90 days, 1 year, 3 years, and 5 years. In addition, cumulative incidence of HCC between aspirin user and nonuser was compared among individuals without HTN, smoking history, alcohol consumption, or DM using Kaplan–Meier plot and log-rank test.

Furthermore, to reduce the effect of selection bias and potential confounding between aspirin users and nonusers, a logistic regression model was used to calculate propensity scores based on age, sex, HTN, DM, dyslipidemia, liver cirrhosis, AVT against CHB, metformin use, statin use, smoking history, alcohol consumption, and obesity, and the nearest method was used for propensity score matching (PSM) analysis between the 2 groups with a ratio of 1:4. The absolute standardized mean difference was used to examine the balance of covariate distribution between aspirin users and nonusers (18). The cumulative incidences of HCC and mortality between aspirin users and nonusers in the PSM cohort were plotted using the Kaplan–Meier method. The difference in HCC and mortality between the 2 groups was compared using the log-rank test.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and R software version 4.0.3 (http://cran.r-project.org/). Two-tailed P values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the entire population and after PSM

According to the enrollment criteria, 161,673 participants with 1,218,026 person-years (PY) were recruited for data analysis. Baseline characteristics of the entire cohort are summarized in Table 1. The mean age was 51.8 ± 8.2 years with a slight male predominance of 57.2%. Aspirin users were older (58.25 vs 51.41) and more likely to have HTN (88.0 vs 33.1%), DM (45.2 vs 18.1%), dyslipidemia (48.6 vs 30.8%), metformin use (28.4 vs 7.32%), statin use (48.3 vs 10.3%), and heavy alcohol consumption (25.7 vs 21.7%) when compared with nonusers (all $P < 0.001$).

PSM with a 1:4 ratio provided 9,837 pairs, with 9,837 aspirin users and 39,348 nonusers. Although the P values of most variables were below 0.001 after PSM, the absolute standardized mean difference was below 0.1, except for statin use, implying that the overall balance of covariate distribution was validated (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C472).

Clinical outcomes in terms of the risk of HCC development and all-cause mortality according to aspirin use

During the follow-up, 7,083 new HCC cases were identified, 385 (3.91%) of whom were aspirin users and 6,698 (4.41%) were nonusers. The median follow-up period of aspirin user and nonuser was both 7.92 years. The cumulative incidence of HCC on aspirin user and nonuser was 1.7% (1.4–1.9) and 2.1% (2.0–2.1), respectively ($P < 0.001$). The average incidence rate of HCC in the entire cohort was 581 per 100,000 PY (95% CI: 568–595 per 100,000 PY). The average incidence rate of HCC was 517 per 100,000 PY (95% CI: 468–571 per 100,000 PY) in the aspirin user group and 586 per 100,000 PY (95% CI: 572–600 per 100,000 PY) in the nonuser group ($P = 0.019$). In the entire cohort, the crude HR for HCC in aspirin users in comparison with nonusers was 0.88 (95% CI: 0.79–0.97; $P = 0.013$). The adjusted HRs in the multivariable Cox proportional hazard model and the FGR model were 0.83 (95% CI: 0.75–0.93; $P = 0.001$) and 0.84 (95% CI: 0.76–0.94; $P = 0.002$), respectively (Table 2).

In the PS-matched cohort, such a relationship was slightly attenuated but consistently reproduced. The crude HR of HCC after aspirin use was 0.72 (95% CI: 0.65–0.80; $P < 0.001$). The adjusted HRs in the Cox proportional hazard model and FGR model were 0.86 (95% CI: 0.77–0.96; $P = 0.006$) and 0.87 (95% CI: 0.78–0.97; $P = 0.01$), respectively (Table 2). An additional time lag of 6, 12, and 24 months did not attenuate the relationship between aspirin use and HCC incidence (HR = 0.88 [95% CI: 0.78–0.98; $P = 0.017$] for 6 months; HR = 0.87 [95% CI: 0.77–0.98; $P = 0.021$] for 12 months; and HR = 0.86 [95% CI: 0.75–0.99; $P = 0.035$] for 24 months; see Supplementary Table 3, Supplementary Digital Content 4, http://links.lww.com/AJG/C475).

Adjusted HRs of liver-related and all-cause mortality in the multivariable Cox proportional hazard model are presented in Table 3. Aspirin use was not associated with the risk of all-cause mortality (HR = 0.93, 95% CI: 0.83–1.04; $P = 0.192$), whereas it was associated with the risk of liver-related mortality (HR = 0.79,

Table 1. Baseline characteristics of participants in the entire and PS-matched cohort by aspirin use

	The entire cohort (n = 161,673)			PS-matched cohort (n = 49,185)		
	Aspirin user (n = 9,837)	Nonuser (n = 151,836)	*P*	Aspirin user (n = 9,837)	Nonuser (n = 39,348)	*P*
Age	58.25 (8.71)	51.41 (8.02)	<0.001	58.25 (8.71)	56.99 (8.37)	<0.001
Sex			<0.001			0.693
Male	5,984 (60.83)	86,485 (56.96)		5,984 (60.83)	23,848 (60.61)	
Female	3,853 (39.17)	65,351 (43.04)		3,853 (39.17)	15,500 (39.39)	
Hypertension			<0.001			0.002
No	1,182 (12.02)	101,583 (66.9)		1,182 (12.02)	4,288 (10.90)	
Yes	8,655 (87.98)	50,253 (33.1)		8,655 (87.98)	35,060 (89.10)	
Diabetes mellitus			<0.001			<0.001
No	5,387 (54.76)	124,337 (81.89)		5,387 (54.76)	24,412 (62.04)	
Yes	4,450 (45.24)	27,499 (18.11)		4,450 (45.24)	14,936 (37.96)	
Dyslipidemia			<0.001			<0.001
No	5,053 (51.37)	105,008 (69.16)		5,053 (51.37)	21,923 (55.72)	
Yes	4,784 (48.63)	46,828 (30.84)		4,784 (48.63)	17,425 (44.28)	
Liver cirrhosis			<0.001			<0.001
No	8,251 (83.88)	118,317 (77.92)		8,251 (83.88)	31,765 (80.73)	
Yes	1,586 (16.12)	33,519 (22.08)		1,586 (16.12)	7,583 (19.27)	
Antiviral therapy			<0.001			<0.001
No	7,299 (74.20)	94,267 (62.08)		7,299 (74.20)	27,515 (69.93)	
Yes	2,538 (25.80)	57,569 (37.92)		2,538 (25.80)	11,833 (30.07)	
Metformin use			<0.001			<0.001
No	7,039 (71.56)	140,722 (92.68)		7,039 (71.56)	31,486 (80.02)	
Yes	2,798 (28.44)	11,114 (7.32)		2,798 (28.44)	7,862 (19.98)	
Statin use			<0.001			<0.001
No	5,090 (51.74)	136,276 (89.75)		5,090 (51.74)	27,462 (69.79)	
Yes	4,747 (48.26)	15,560 (10.25)		4,747 (48.26)	11,886 (30.21)	
Smoking history			<0.001			0.25
Nonsmoker	5,590 (56.83)	90,778 (59.79)		5,590 (56.83)	22,583 (57.39)	
Ex-smoker	2,247 (22.84)	29,303 (19.30)		2,247 (22.84)	8,681 (22.06)	
Current smoker	2,000 (20.33)	31,755 (20.91)		2,000 (20.33)	8,084 (20.55)	
Alcohol drink			<0.001			0.291
No	7,305 (74.26)	118,922 (78.32)		7,305 (74.26)	29,426 (74.78)	
Yes	2,532 (25.74)	32,914 (21.68)		2,532 (25.74)	9,922 (25.22)	
Obesity			<0.001			<0.001
Underweight	76 (0.77)	3,414 (2.25)		76 (0.77)	407 (1.03)	
Normal	2,115 (21.5)	55,728 (36.7)		2,115 (21.5)	9,006 (22.89)	
Overweight	2,503 (25.44)	40,379 (26.59)		2,503 (25.44)	10,490 (26.66)	
Obese	5,143 (52.28)	52,315 (34.45)		5,143 (52.28)	19,445 (49.42)	

Data are presented as mean (SD) or n (%).
PS, propensity score.

95% CI: 0.64–0.96, $P = 0.019$). The cumulative incidence plots of HCC and all-cause mortality are shown in Figure 2. The cumulative incidence of HCC in the aspirin user group was significantly lower than that in the nonuser group in the matched cohort ($P < 0.001$), whereas the cumulative incidence of all-cause mortality was not significantly different between the 2 groups.

Table 2. Multivariate Cox proportional hazard/Fine and Gray Regression analysis of HCC

	The entire cohort				PS-matched cohort			
	Cox proportional hazard		Fine and Gray		Cox proportional hazard		Fine and Gray	
	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Aspirin use								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.83 (0.75–0.93)	0.001	0.84 (0.76–0.94)	0.002	0.86 (0.77–0.96)	0.006	0.87 (0.78–0.96)	0.010
Age	1.05 (1.04–1.05)	<0.001	1.04 (1.04–1.05)	<0.001	1.04 (1.03–1.04)	<0.001	1.04 (1.03–1.04)	<0.001
Sex								
Female	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Male	1.72 (1.61–1.84)	<0.001	1.71 (1.60–1.83)	<0.001	1.59 (1.41–1.78)	<0.001	1.57 (1.40–1.76)	<0.001
Hypertension								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	1.14 (1.08–1.20)	<0.001	1.14(1.08–1.20)	<0.001	1.30 (1.11–1.52)	0.002	1.30 (1.11–1.53)	0.001
Diabetes mellitus								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	1.51 (1.42–1.60)	<0.001	1.48 (1.39–1.57)	<0.001	1.41 (1.29–1.55)	<0.001	1.38 (1.26–1.52)	<0.001
Dyslipidemia								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.79 (0.75–0.84)	<0.001	0.81 (0.76–0.85)	<0.001	0.73 (0.67–0.80)	<0.001	0.74 (0.68–0.82)	<0.001
Liver cirrhosis								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	7.96 (7.55–8.39)	<0.001	7.85 (7.43–8.30)	<0.001	6.94 (6.37–7.57)	<0.001	6.82 (6.22–7.48)	<0.001
Antiviral therapy								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.74 (0.71–0.78)	<0.001	0.76 (0.72–0.80)	<0.001	0.90 (0.82–0.98)	0.011	0.92 (0.84–1.01)	0.078
Metformin use								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.80 (0.73–0.88)	<0.001	0.81 (0.74–0.89)	<0.001	0.79 (0.70–0.89)	<0.001	0.81 (0.71–0.91)	<0.001
Statin use								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.47 (0.42–0.52)	<0.001	0.47 (0.42–0.53)	<0.001	0.50 (0.44–0.56)	<0.001	0.50 (0.44–0.56)	<0.001
Smoking history								
Nonsmoker	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Ex-smoker	1.14 (1.06–1.22)	<0.001	1.14 (1.06–1.22)	<0.001	1.20 (1.07–1.34)	0.002	1.20 (1.07–1.34)	0.002
Current smoker	1.66 (1.56–1.78)	<0.001	1.64 (1.53–1.75)	<0.001	1.74 (1.55–1.95)	<0.001	1.70 (1.51–1.91)	<0.001
Alcohol drink								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	1.29 (1.22–1.37)	<0.001	1.29 (1.22–1.37)	<0.001	1.20 (1.09–1.33)	0.001	1.21 (1.10–1.33)	<0.001
Obesity								
Underweight	0.92 (0.77–1.10)	0.369	0.90 (0.74–1.08)	0.241	0.47 (0.27–0.82)	0.008	0.45 (0.26–0.78)	0.005
Normal	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Overweight	1.11 (1.05–1.18)	0.001	1.12 (1.05–1.19)	<0.001	1.15 (1.02–1.28)	0.019	1.16 (1.03–1.30)	0.012
Obese	1.17 (1.10–1.24)	<0.001	1.18 (1.11–1.25)	<0.001	1.17 (1.06–1.30)	0.003	1.18 (1.07–1.31)	0.001

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; PS, propensity score.

Table 3. Multivariate Cox proportional hazard analysis of all-cause and liver-related mortality

	All-cause mortality		Liver-related mortality	
	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Aspirin use				
No	1.00 (reference)		1.00 (reference)	
Yes	0.93 (0.83–1.04)	0.192	0.79 (0.64–0.96)	0.019
Age	1.08 (1.08–1.09)	<0.001	1.06 (1.05–1.06)	<0.001
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.71 (1.58–1.85)	<0.001	1.86 (1.64–2.11)	<0.001
Hypertension				
No	1.00 (reference)		1.00 (reference)	
Yes	1.19 (1.12–1.27)	<0.001	1.11 (1.01–1.22)	<0.001
Diabetes mellitus				
No	1.00 (reference)		1.00 (reference)	
Yes	1.93 (1.80–2.07)	<0.001	1.79 (1.61–2.00)	<0.001
Dyslipidemia				
No	1.00 (reference)		1.00 (reference)	
Yes	0.59 (0.55–0.64)	<0.001	0.59 (0.52–0.66)	<0.001
Liver cirrhosis				
No	1.00 (reference)		1.00 (reference)	
Yes	3.55 (3.34–3.77)	<0.001	10.89 (9.83–12.06)	<0.001
Hepatitis B treatment				
No	1.00 (reference)		1.00 (reference)	
Yes	0.45 (0.42–0.48)	<0.001	0.39 (0.36–0.43)	<0.001
Metformin use				
No	1.00 (reference)		1.00 (reference)	
Yes	0.68 (0.61–0.76)	<0.001	0.82 (0.70–0.97)	0.017
Statin use				
No	1.00 (reference)		1.00 (reference)	
Yes	0.58 (0.51–0.65)	<0.001	0.40 (0.32–0.50)	<0.001
Smoking history				
Nonsmoker	1.00 (reference)		1.00 (reference)	
Ex-smoker	1.03 (0.94–1.13)	0.513	1.02 (0.89–1.16)	0.774
Current smoker	1.92 (1.77–2.09)	<0.001	1.87 (1.66–2.11)	<0.001
Alcohol drink				
No	1.00 (reference)		1.00 (reference)	
Yes	1.14 (1.06–1.22)	0.001	1.33 (1.20–1.48)	<0.001
Obesity				
Underweight	1.73 (1.49–2.01)	<0.001	1.29 (0.98–1.70)	0.073
Normal	1.00 (reference)		1.00 (reference)	
Overweight	0.85 (0.79–0.92)	<0.001	1.02 (0.91–1.14)	0.710
Obese	0.88 (0.82–0.94)	<0.001	1.09 (0.98–1.21)	0.120

CI, confidence interval; HR, hazard ratio.

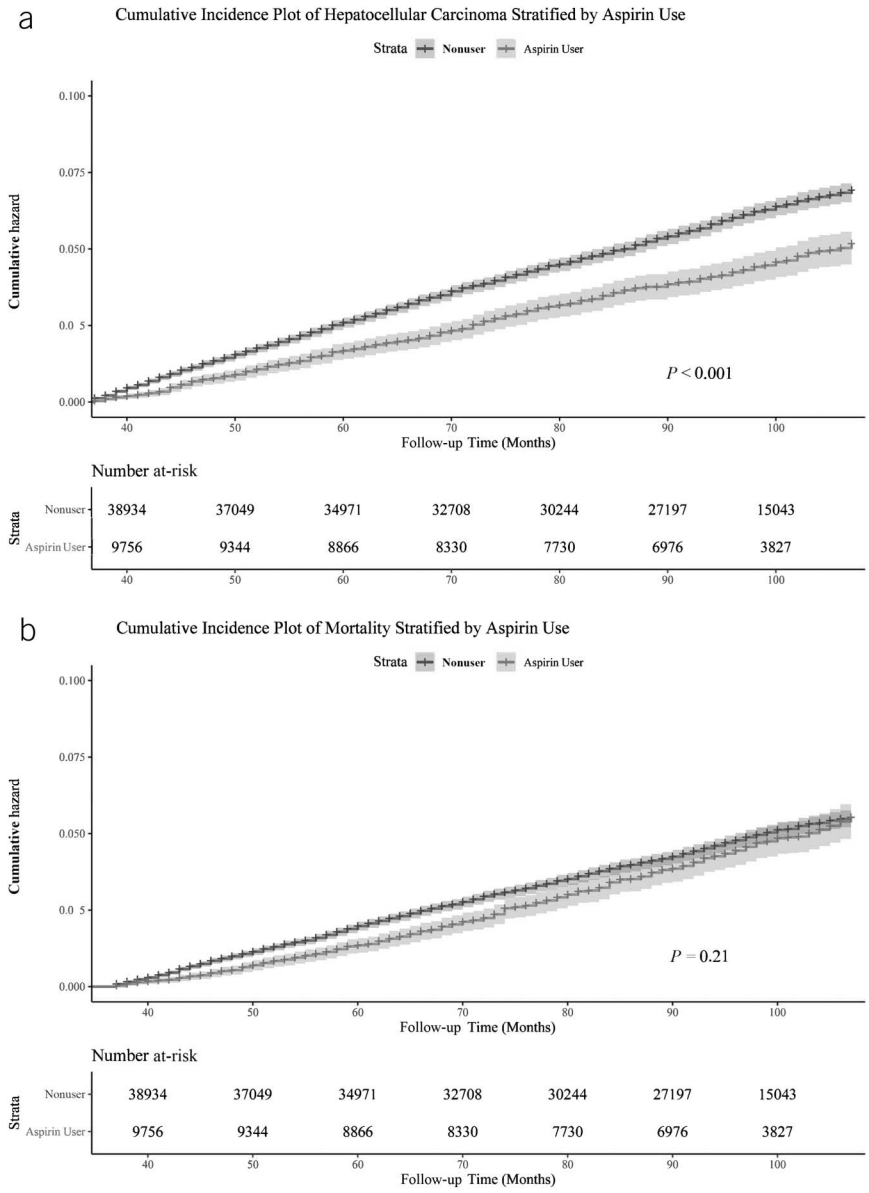

Figure 2. Cumulative incidence plots of hepatocellular carcinoma (**a**) and mortality (**b**) stratified by aspirin use in the matched cohort.

Subgroup analyses

The relationship between aspirin use and the risk of HCC occurrence was statistically significant in the subgroups with liver cirrhosis, both sexes, HTN, non-DM, non-AVT against CHB, nonmetformin use, nonstatin use, both smoking histories, and obesity. Adjusted HRs (95% CIs) of HCC with the detailed content of each subgroup are shown in Figure 3. We additionally conducted analysis with patient groups without HTN, smoking, alcohol, or DM. The cumulative incidence plots of aspirin and HCC in each group were plotted using the Kaplan–Meier method. The plots are shown in Supplementary Figure 2 (see Supplementary Digital Content 2, http://links.lww.com/AJG/C473). In all 4 groups, aspirin user showed trends toward lower incidence of HCC compared with nonuser. Statistical significance was observed only in the non-DM group ($P = 0.031$), whereas marginal significance was observed in nonsmoking ($P = 0.067$) and nonalcohol ($P = 0.069$) groups. The non-HTN group did not present significant association between aspirin and HCC ($P = 0.370$), which could be interpreted as type II error, maybe primarily owing to imbalance of sample size between 2 groups.

Moreover, after adjusting coinfection with HDV, which was 6.6% (n = 10,664) of the entire population, the adjusted HR (95% CIs) was 0.84 (0.76–0.94; $P = 0.002$) in the FGR model. In addition, using different criteria according to treatment duration among aspirin user, i.e., ≥90 days, ≥1 year, ≥3 years, and ≥5 years, there was a trend of negative correlation between longer duration of aspirin use and incidence of HCC (P for trend <0.001, see Supplementary Table 4, Supplementary Digital Content 4, http://links.lww.com/AJG/C475). In particular, the HCC risk among aspirin users defined based on at least 5-year treatment duration was significantly lower compared with aspirin nonusers with adjusted HR of 0.78 (95% CI: 0.66–0.92; $P = 0.003$) (see Supplementary Table 4, Supplementary Digital Content 4, http://links.lww.com/AJG/C475). Moreover, aspirin use was negatively

	Aspirin user	Nonuser	Adjusted HR(95% CI)	*P* value
	N of HCC/N at risk	*N of HCC/N at risk*		
Cirrhosis				
Yes	217/1586	4630/33519	0.81 (0.70–0.94)	0.004
No	168/8251	2068/118317	0.88 (0.74–1.04)	0.122
Sex				
Male	294/5984	5016/86485	0.87 (0.77–0.99)	0.03
Female	91/3853	1682/65351	0.76 (0.61–0.95)	0.018
Hypertension				
Yes	348/8655	2718/50253	0.86 (0.76–0.96)	0.009
No	37/1182	3980/101583	0.91 (0.66–1.27)	0.584
Diabetes mellitus				
Yes	207/4450	1846/27499	0.95 (0.82–1.11)	0.381
No	178/5387	4852/124337	0.76 (0.65–0.89)	0.001
Dyslipidemia				
Yes	134/4784	1519/46828	0.9 (0.75–1.08)	0.266
No	251/5053	5179/105008	0.82 (0.72–0.94)	0.004
Hepatitis B treatment				
Yes	148/2538	2904/57569	0.88 (0.74–1.04)	0.141
No	237/7299	3794/94267	0.86 (0.75–0.99)	0.035
Metformin use				
Yes	123/2798	567/11114	1.09 (0.89–1.34)	0.42
No	262/7039	6131/140722	0.77 (0.68–0.88)	<0.001
Statin use				
Yes	113/4747	277/15560	1.02 (0.81–1.29)	0.864
No	272/5090	6421/136276	0.80 (0.71–0.91)	0.001
Smoking history				
Yes	210/4247	3711/61058	0.85 (0.73–0.98)	0.026
No	175/5590	2987/90778	0.84 (0.71–0.98)	0.03
Alcohol drink				
Yes	119/2532	1878/32914	0.87 (0.72–1.06)	0.181
No	266/7305	4820/118922	0.98 (0.86–1.12)	0.754
Obesity				
Above Overweight	307/7646	4458/92694	0.86 (0.76–0.97)	0.015
Below Normal	78/2191	2240/59142	0.79 (0.62–1.00)	0.05

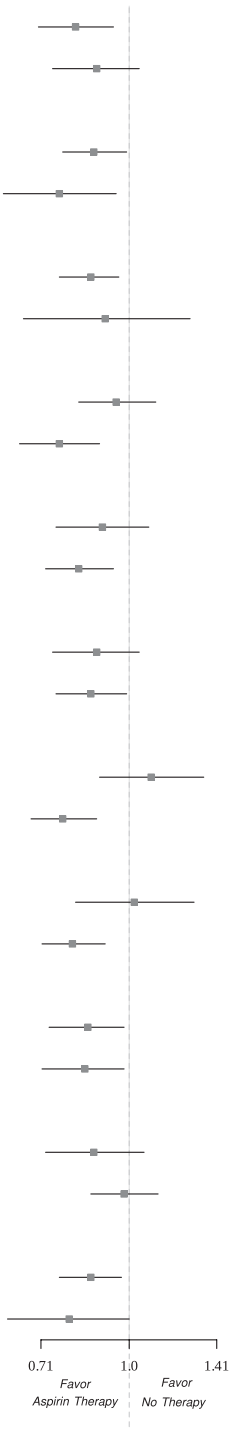

Figure 3. Subgroup analysis of hepatocellular carcinoma by aspirin use. CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio.

associated with HCC incidence when stratified by duration of aspirin use (per 6 months) (adjusted HR 0.97 [95% CI: 0.96–0.98], $P < 0.001$). From interaction analysis of aspirin and statin use on HCC, users of both aspirin and statin, only statin user, and only aspirin user presented adjusted HRs (95% CIs) of 0.45 (0.67–0.54; $P < 0.001$), 0.45 (0.40–0.51; $P < 0.001$), and 0.80 (0.71–0.91; $P = 0.001$), compared with nonuser (see Supplementary Table 5, Supplementary Digital Content 4, http://links.lww.com/AJG/C475). In addition, aspirin use was not significantly associated with all-cause mortality in both DM and non-DM groups with

adjusted HR (95% CI) of 0.95 (0.81–1.11; $P = 0.481$) and 0.93 (0.80–1.09; $P = 0.358$), respectively.

DISCUSSION

In this study, aspirin use showed a protective association with HCC incidence. The subsequent stratification analysis indicated that aspirin might be associated with a reduced risk of HCC in subgroups with liver cirrhosis, both sexes, HTN, non-DM, non-AVT against CHB, nonmetformin use, nonstatin use, past and current smoking histories, and obesity. Moreover, the result found out the significant association between aspirin use and decreased risk of liver-related mortality, which was different from all-cause mortality.

The results of our study are similar to those of previous studies in East Asia. In addition to the nationwide study of Taiwan mentioned above, Lee et al. (14) conducted a study of relationships between antiplatelet therapies, especially aspirin, and HCC in the Republic of Korea and reported a significant protective association. Our study showed the same direction of protective association of aspirin on HCC while compensating for the small sample size from 1 institution used by Lee et al.

Notably, we observed that the association of aspirin with the reduced risk of HCC differed based on comedications. HBV-related HCC primarily originates from an inflammation-induced vicious cycle involving hepatocyte damage, necroinflammation, regeneration, fibrosis, and genomic instability (19–22). Therefore, its association seems theoretically plausible, considering that aspirin has primarily antiplatelet and anti-inflammatory effects by inhibiting protein kinase 3 and nuclear factor κB signaling (23,24). However, comedications with statins or metformin presented reverse associations. Statins, which downregulate reactive oxygen species formation and upregulate anti-inflammatory effectors (25), and metformin, which inhibits nuclear factor κB through AMP-activated protein kinase-dependent and independent pathways (26,27), are anticancer medications related to anti-inflammatory mechanisms. Considering similar mechanisms of anticarcinogenic effect, statins, and metformin could act as effect modifiers on the association of aspirin and reduced risk of HCC, especially in patients with CHB. It implies that the prescription of aspirin solely for preventing HCC risk among patients with CHB in routine practice might be reserved for selected cases that may benefit from long-term aspirin use according to the individualized risk and benefit. Moreover, interaction analyses between aspirin and statin use on HCC presented that aspirin use and statin use might not have any additive effect. The comprehensive analyses of aspirin and statin use on HCC showed aspirin use is associated with a reduced risk of HCC incidence in nonstatin users, not statin users; however, a well-designed prospective study should be further implemented to clarify the exact relationship.

The association of reduced risk of HCC with aspirin was maintained even after adjusting for liver cirrhosis favoring aspirin use, regardless of liver cirrhosis. Nevertheless, the stratification analysis showed a different pattern; the HR was 0.88 (95% CI: 0.74–1.04; $P = 0.1224$) among patients without liver cirrhosis. This is most likely due to the relatively small proportion of aspirin usage in such a stratum, i.e., 6.5% of patients (8,251 of 126,568 patients), compared with 44.1% in a study conducted in the United States (12). Thus, in the simulation, increasing the number of aspirin users while maintaining the ratio of HCC incidence and HR of each group would result in a P value of <0.05 when the proportion of aspirin users reaches 11.0%. Consistent with this finding, the meta-regression analysis by Memel et al. (1) indicated that a high proportion of aspirin users should increase the statistical power for assessing the protective association between aspirin use and HCC incidence. More comprehensive intervention studies with large numbers of aspirin users should be implemented to clarify the association between aspirin use and HCC risk.

Aspirin use might inherently increase the potential hazard of bleeding, especially considering the bleeding tendency in chronic liver disease, because of lower platelet counts and prolonged prothrombin time (28,29). Although a study conducted with patients with HBV infection in the Republic of Korea showed that aspirin alone was not significantly associated with an increased risk of bleeding (HR = 1.11 [95% CI: 0.48–2.54]), the study did not clarify the dose and duration of aspirin (14). Nevertheless, our study excluded severe liver cirrhosis patients with complications, who are considered to have strong bleeding tendency, and the protective association found in our study suggests that aspirin might be carefully prescribed to patients with chronic HBV infection for primary prevention after weighing the advantages and disadvantages individually.

Our study has several strengths. First, the protective association of aspirin use among Asian CHB patients with liver cirrhosis has rarely been analyzed (1). There are only 2 cohort studies to date; one with 204 patients with cirrhosis recruited from a single institute (14) and the other with 1,810 patients with cirrhosis recruited from the Taiwan nationwide cohort (11). Our incomparably large sample size of patients with HBV-related cirrhosis, i.e., 35,105 patients in the entire cohort and 9,169 patients in the PS-matched cohort, allowed us to closely investigate the association between aspirin use and HCC risk. The favorable effect of aspirin on specific strata was inconsistent; heterogeneity in study designs and population characteristics, as well as variable interactions with comorbidities and/or medications, might be partly responsible for such discrepancies. Second, various statistical methods were applied to strengthen the scientific reliability. As per the World Trade Center Health Program in Centers for Disease Control (15), a minimum latency of 4 years is recommended to assess the risk of developing solid cancers. Accordingly, we set a 3-year lag to both aspirin users and nonusers and subsequently applied an additional time lag of 6, 12, and 24 months, reproducing similar results. Moreover, to minimize the indication bias of aspirin, its definite conventional indications (e.g., myocardial infarction and ischemic stroke) and contraindications (e.g., decompensated liver cirrhosis) were excluded at baseline (30). Overall, a well-balanced PSM with additional multivariable analyses helped to draw a robust conclusion. Third, because the NHIS, as a single insurer run by the government of Republic of Korea, covers 97.2% of the entire population in the Republic of Korea (31), this database can be accepted as literally "nationwide" (32,33). The validation of the NHIS data set using a combination of *ICD-10* codes showed a positive predictive value of 97.5% (96.1–98.5), with the lowest error rate of 4.2% for cases of inflammatory bowel disease in the Republic of Korea (34). Our study, with a representative cohort of the population in the Republic of Korea, provides strong evidence of a protective association of aspirin on HCC. In addition, we found that the association of heavy alcohol consumption on increased risk of HCC was significant ($P < 0.001$, see Supplementary Figure 3, Supplementary Digital Content 3, http://links.lww.com/AJG/C474), suggesting the clinical importance of life style among at-risk population.

Study Highlights

WHAT IS KNOWN

- ✓ Hepatitis B virus (HBV) infection is a crucial causative factor for the development of hepatocellular carcinoma (HCC).
- ✓ Aspirin may have a protective association on hepatocellular carcinoma.
- ✓ The benefits of aspirin use among HBV-infected patients are unclear.

WHAT IS NEW HERE

- ✓ Long-term aspirin use is associated with a decreased incidence of HCC in the HBV-infected population.
- ✓ Several considerable clinical indications of long-term aspirin on reducing HCC incidence were examined.

Our study has some limitations. First, our observational study design could not clarify a causal association of aspirin with HCC risk. To overcome this limitation, we attempted to adjust potential confounding variables and to exclude the compelling indication of aspirin as much as possible. Furthermore, we used a quasi-experimental study design with PSM, and it confirmed the same direction of relationship with statistical significance. Nevertheless, an observational study related to medication has inherently a limitation of indication bias, which included use of aspirin, statin, and metformin in this study. Further interventional or experimental studies are required to resolve this issue. Second, considering that the use of aspirin is based on a number of factors such atherosclerotic cardiovascular disease, risks, severity of portal HTN, bleeding risks, and specific indication for aspirin use, our nationwide database had a limitation of being subject to biased interpretation. Third, in the Republic of Korea, most patients were infected with HBV genotype C2 through vertical transmission, both of which were associated with a higher risk of HCC development (35). Thus, our results might not be generalizable to other ethnicities. Finally, because of incompleteness of the nationwide registry-based cohort, there was a lack of information on hepatitis B e antigen or aspirin dosage. However, because aspirin use was independently associated with lower risk of HCC through multivariable analyses adjusting for various key factors such as age, sex, DM, alcohol, AVT, and liver cirrhosis from our large-scale nationwide cohort, incorporation of hepatitis B e antigen into analyses is not likely to have attenuated the statistical significance of aspirin use. In terms of daily aspirin dosage, when we examined the prescription statement of aspirin from National Sample Cohort Database, about 99% of prescribed aspirin had a daily dosage of 100 mg or less, minimizing bias.

In conclusion, long-term aspirin use is associated with a decreased incidence of HCC in the HBV-infected population. Moreover, several considerable clinical indications of aspirin on reducing HCC incidence were explored with subgroup analyses. More comprehensive studies with interventional or experimental designs are required to establish the causality between aspirin use and hepatocarcinogenesis.

CONFLICTS OF INTEREST

Guarantor of the article: Beom Kyung Kim, MD, PhD.

Specific author contributions: J.Y. and B.K.K. designed the study. B.Y., S.H.A., and B.K.K. performed the literature search and review. B.Y. and J.Y. conducted the data analysis. B.Y. and B.K.K. drafted the manuscript. J.Y., S.H.A., and B.K.K. revised the manuscript. All authors have read and approved the final version of the manuscript.

Financial support: This work was supported by the Korea Health Industry Development Institute through "Social and Environmental Risk Research" funded by the Ministry of Health & Welfare (HI19C0052, URL: https://www.khidi.or.kr/kps).

Potential competing interests: None to report.

Data availability: Data and study materials are not able to be available to other researchers.

REFERENCES

1. Memel ZN, Arvind A, Moninuola O, et al. Aspirin use is associated with a reduced incidence of hepatocellular carcinoma: A systematic review and meta-analysis. Hepatol Commun 2021;5:133–43.
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88–98.
3. Park SH, Plank LD, Suk KT, et al. Trends in the prevalence of chronic liver disease in the Korean adult population, 1998-2017. Clin Mol Hepatol 2020;26:209–15.
4. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
5. Thomas DL. Global elimination of chronic hepatitis. N Engl J Med 2019;380:2041–50.
6. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: Reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet 2018;392:2052–90.
7. Yim HJ, Kim JH, Park JY, et al. Comparison of clinical practice guidelines for the management of chronic hepatitis B: When to start, when to change, and when to stop. Clin Mol Hepatol 2020;26:411–29.
8. Da Fonseca LG, Forner A. Editorial: Aspirin and NSAID for chemoprevention of hepatocellular carcinoma-ready for their use? Aliment Pharmacol Ther 2021;54:850–1.
9. Aiolfi R, Sitia G. Chronic hepatitis B: Role of anti-platelet therapy in inflammation control. Cell Mol Immunol 2015;12:264–8.
10. Li T, Dong ZR, Guo ZY, et al. Aspirin enhances IFN-α-induced growth inhibition and apoptosis of hepatocellular carcinoma via JAK1/STAT1 pathway. Cancer Gene Ther 2013;20:366–74.
11. Lee TY, Hsu YC, Tseng HC, et al. Association of daily aspirin therapy with risk of hepatocellular carcinoma in patients with chronic hepatitis B. JAMA Intern Med 2019;179:633–40.
12. Simon TG, Ma Y, Ludvigsson JF, et al. Association between aspirin use and risk of hepatocellular carcinoma. JAMA Oncol 2018;4:1683–90.
13. Simon TG, Duberg AS, Aleman S, et al. Association of aspirin with hepatocellular carcinoma and liver-related mortality. N Engl J Med 2020;382:1018–28.
14. Lee M, Chung GE, Lee JH, et al. Antiplatelet therapy and the risk of hepatocellular carcinoma in chronic hepatitis B patients on antiviral treatment. Hepatology 2017;66:1556–69.
15. Howard J. Minimum Latency & Types or Categories of Cancer. World Trade Center Health Program, Centers for Disease Control and Prevention: Geneva, Switzerland, 2015.
16. Zhou Z, Rahme E, Abrahamowicz M, et al. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: A comparison of methods. Am J Epidemiol 2005;162:1016–23.
17. Misra A. Ethnic-specific criteria for classification of body mass index: A perspective for Asian Indians and American Diabetes Association Position statement. Diabetes Technol Ther 2015;17:667–71.
18. Zhang Z, Kim HJ, Lonjon G, et al. Balance diagnostics after propensity score matching. Ann Transl Med 2019;7:16.
19. Pavlovic N, Rani B, Gerwins P, et al. Platelets as key factors in hepatocellular carcinoma. Cancers (Basel) 2019;11:1022.
20. Iannacone M, Sitia G, Isogawa M, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 2005;11:1167–9.
21. Maini MK, Schurich A. Platelets harness the immune response to drive liver cancer. Proc Natl Acad Sci USA 2012;109:12840–1.

22. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73.
23. Chan TA, Morin PJ, Vogelstein B, et al. Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis. Proc Natl Acad Sci USA 1998;95:681–6.
24. Leng J, Han C, Demetris AJ, et al. Cyclooxygenase-2 promotes hepatocellular carcinoma cell growth through Akt activation: Evidence for Akt inhibition in celecoxib-induced apoptosis. Hepatology 2003;38:756–68.
25. Forrester JS, Libby P. The inflammation hypothesis and its potential relevance to statin therapy. Am J Cardiol 2007;99:732–8.
26. Chaudhary R, Bliden KP, Garg J, et al. Statin therapy and inflammation in patients with diabetes treated with high dose aspirin. J Diabetes Complications 2016;30:1365–70.
27. Saisho Y. Metformin and inflammation: Its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets 2015;15:196–205.
28. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: A systematic review and meta-analysis. JAMA 2019;321:277–87.
29. Tripodi A. Hemostasis in acute and chronic liver disease. Semin Liver Dis 2017;37:28–32.
30. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol 2006;98:253–9.
31. Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. Diabetes Metab J 2014;38:395–403.
32. Kim D, Yang PS, Sung JH, et al. Less dementia after catheter ablation for atrial fibrillation: A nationwide cohort study. Eur Heart J 2020;41:4483–93.
33. Choi J, Kim HJ, Lee J, et al. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: A Korean nationwide cohort study. JAMA Oncol 2019;5:30–6.
34. Lee CK, Ha HJ, Oh SJ, et al. Nationwide validation study of diagnostic algorithms for inflammatory bowel disease in Korean National Health Insurance Service database. J Gastroenterol Hepatol 2020;35:760–8.
35. Kim BJ. Hepatitis B virus mutations related to liver disease progression of Korean patients. World J Gastroenterol 2014;20:460–7.