

Aspirin Reduces the Incidence of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Receiving Oral Nucleos(t)ide Analog

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INTRODUCTION: Aspirin may reduce the risk of chronic hepatitis B (CHB)-related hepatocellular carcinoma (HCC) in patients receiving antiviral treatment. We aimed to investigate the impact of aspirin on reducing HCC risk in patients treated with first-line oral nucleos(t)ide analogs (NAs; entecavir and/or tenofovir disoproxil fumarate).

METHODS: We conducted a territorywide, retrospective cohort study in NA-treated CHB patients between 2000 and 2018 from the electronic healthcare data repository in Hong Kong. Subjects were classified into aspirin users for at least 90 days during NA treatment (aspirin group) or no aspirin or any other antiplatelet use during follow-up period (no aspirin group). Incidence rates of HCC and gastrointestinal bleeding (GIB) in 2 groups with propensity score matching with 1:3 ratio.

RESULTS: Of 35,111 NA-treated CHB patients of mean age of 53.0 years and 61.6% men, sixty-nine (4.0%) and 1,488 (4.5%) developed HCC at a median (interquartile range) of 2.7 (1.4–4.8) years and 3.2 (1.8–6.0) years in the aspirin group and no aspirin group, respectively. A duration-dependent association between aspirin and the risk of HCC was observed (subhazard ratio [sHR] 3 months–2 years: 0.65; 95% confidence interval [CI] 0.47–0.92; sHR 2–5 years: 0.63; 95% CI 0.43–0.94; sHR from ≥5 years: 0.41; 95% CI 0.18–0.91). Patients who took aspirin for ≤2 years had significantly higher risk of GIB (sHR: 1.73, 95% CI 1.07–2.79) than those not receiving aspirin. The risk of GIB started declining with the longer use of aspirin and becoming insignificant for ≥5 years' use (sHR: 0.79, 95% CI 0.19–3.21).

DISCUSSION: Long-term aspirin use is associated with a lower risk of HCC in a duration-dependent manner in NA-treated CHB patients without a significant increase in the risk of gastrointestinal adverse effects.

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/CTG/A535>; <http://links.lww.com/CTG/A536>; <http://links.lww.com/CTG/A537>; <http://links.lww.com/CTG/A538>; <http://links.lww.com/CTG/A539>.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide (1,2). More than 500,000 new cases of HCC are diagnosed annually (2). Hepatitis B virus (HBV) infection is a crucial risk factor for HCC, and chronic hepatitis B (CHB)-related HCC is prevalent in Asia because of the endemicity of this chronic viral infection (3). Although antiviral treatment with oral nucleos(t)ide analogs (NAs) (4–6) effectively inhibits the replication of HBV, the risk of HCC is not completely

abolished (7). Therefore, using NA alone may not suffice to prevent HCC, and hence, other effective strategies of chemoprophylaxis for HCC is warranted.

Most studies such as a recent article by Simon et al. reported that the use of low-dose aspirin was associated with a significantly lower risk of HCC and liver-related mortality than no use of aspirin. However, to date, the chemopreventive effect of aspirin use on HCC remains controversial (8–10). For example, a 11-year follow-up of a US randomized control trial claimed no beneficial

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effects from aspirin use on various cancers (11). Different study designs with limited sample size or variable follow-up durations may account for such conflicting results. Most studies were conducted in Western countries; whether aspirin works as well in Asia where HBV is highly prevalent and the main cause of HCC remains unclear. Furthermore, patients at risk of HCC should be treated with antiviral therapy, and therefore, additional chemopreventive strategy on top may further reduce the risk of HCC in NA-treated CHB patients (4–6,12). In this study, we aimed to investigate the impact of aspirin on HCC risk in patients treated with first-line NAs (entecavir, tenofovir disoproxil fumarate, and/or tenofovir alafenamide). We also reported the gastrointestinal (GI) safety of aspirin use.

METHODS

Study design and data source

A territorywide retrospective cohort study was performed by retrieving data from the Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority, Hong Kong. CDARS facilitates the retrieval of clinical data captured from different operational systems for analysis and reporting and provides high-quality information to support clinical and management decisions by integrating the clinical data resided in data warehouse (13). The electronic healthcare database includes in-patient and out-patient data from all public healthcare services in Hong Kong, which covers approximately 80% of the local population. All clinical information captured in CDARS, including patients' demographics, diagnoses, laboratory results, and use of medications, was anonymized to ensure confidentiality.

Subjects

We evaluated adults aged 18 years or older in Hong Kong with CHB who began taking first-line NAs between September 1, 2005, and December 31, 2018 (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/CTG/A535>). We excluded patients coinfecting with hepatitis C virus or hepatitis D virus based on *International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis codes and/or virological assays; coinfecting with HIV based on *ICD-9-CM* diagnosis codes; had other autoimmune or metabolic liver diseases; and had HCC or liver transplant before or within 180 days from the baseline date. Patients were followed until diagnosis of HCC, censored at death, or the last follow-up date (February 29, 2020). The cohort was divided according to antiplatelet therapy (aspirin group vs no aspirin group). To ensure a new user design, the aspirin group included patients who initiated aspirin for at least 90 days during NA treatment, and the date of their first filled prescription of aspirin (the index date) was after the date of their first filled prescription of NA. The no aspirin group included patients who had never initiated any antiplatelet therapy till their last follow-up date.

Data collection

Data were retrieved from CDARS in March 2020. We defined the baseline date as the first filled prescription of aspirin in the aspirin group and a random index date in the no aspirin group, respectively. Demographics data including sex and date of birth were captured. Hematological and virological parameters, liver and renal biochemistries, relevant diagnoses and procedures, concomitant drugs, and other laboratory parameters were collected at baseline and during follow-up.

Definitions of clinical events and comorbid conditions

We defined HCC based on diagnosis codes (155.0—hepatocellular carcinoma and 155.2—carcinoma of liver) or any HCC treatment (see Supplementary Table 2, Supplementary Digital Content 2, <http://links.lww.com/CTG/A536>). Gastrointestinal bleeding (GIB) was defined based on diagnosis codes. Cirrhosis was defined based on the *ICD-9-CM* diagnosis code for cirrhosis (571/571.2/571.5/571.51/571.52/571.53) (see Supplementary Table 2, Supplementary Digital Content 2, <http://links.lww.com/CTG/A536>). Hypertension was identified by use of any antihypertensive drugs or *ICD-9-CM* diagnosis codes for hypertension (401–404) (see Supplementary Table 2, Supplementary Digital Content 2, <http://links.lww.com/CTG/A536>). Diabetes mellitus was classified by exposure to antidiabetic agents, and/or HbA1c $\geq 6.5\%$, and/or fasting plasma glucose ≥ 7 mmol/L in 2 measurements or ≥ 11.1 mmol/L in 1 measurement, and/or the *ICD-9-CM* diagnosis codes for diabetes mellitus (250–250.93) (see Supplementary Table 2, Supplementary Digital Content 2, <http://links.lww.com/CTG/A536>).

Clinical outcomes

The primary outcome was incident HCC; secondary outcome was incident GIB as the safety endpoint. Competing events were death and liver transplantation for analysis of HCC and death for analysis of GIB.

Statistical analysis

Data were analyzed using Statistical Product and Service Solutions (SPSS) Statistics for Windows, version 25.0 (IBM, Armonk, NY), SAS (9.4; SAS Institute, Cary, NC), and R software (4.0.0; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean \pm SD or median (interquartile range [IQR]), as appropriate, while categorical variables were presented as number (percentage). Qualitative and quantitative differences between subgroups were analyzed by χ^2 or Fisher exact tests for categorical parameters and the Student *t* test or the Mann-Whitney test for continuous parameters, as appropriate. Cumulative incidence function of HCC with adjustment of competing risk of death and liver transplantation was estimated with 95% confidence interval (CI). We used the Gray test to assess differences between the cohorts.

Inappropriate missing data handling would lead to a faulty conclusion by reducing the statistical power of a study and/or creating biased estimates because of selection bias. Random forest-based multivariate imputation by chained equations was performed to minimize imputation error for both continuous and categorical variables (14). The imputed variables (missing percentage) were platelet counts (3.69%), creatinine (4.3%), albumin (2.42%), total bilirubin (2.45%), alanine aminotransferase (ALT) (2.4%), and hepatitis B e antigen status (27.95%). These covariates, together with 12 important baseline characteristics, the event indicator, and Nelson-Aalen estimator of the cumulative hazard at the time of event or censoring, were included in the imputation model.

For multivariable analyzes, hazard ratios (HRs) and 95% CIs for HCC and GIB were estimated using Fine and Gray competing risks regression model, again accounting for competing risks (15). The overall coefficient estimates and SEs were computed by combining the estimates obtained in each individual multiple imputation data set using Rubin rules.

Table 1. Clinical characteristics of patients with chronic hepatitis B according to aspirin use

Clinical characteristics	No aspirin use (N = 33,367)	Aspirin use ^a (N = 1,744)	P value ^b
Age (yr) ^{c,d}	52.5 (12.5)	62.2 (10.8)	<0.001
Male sex, n (%) ^{c,d}	20,414 (61.2)	1,203 (69.0)	<0.001
Cirrhosis, n (%) ^{c,d,e,f}	2,177 (6.5)	197 (11.3)	<0.001
Hypertension, n (%) ^{c,d,e}	7,410 (22.2)	1,105 (63.4)	<0.001
Renal replacement therapy, n (%) ^{c,e}	132 (0.4)	58 (3.3)	<0.001
Diabetes mellitus, n (%) ^{c,d,e}	5,729 (17.2)	662 (38.0)	<0.001
Platelet ($\times 10^9/L$) ^{c,d}	191.5 (69.9)	191.2 (92.4)	0.89
Creatinine ($\mu\text{mol/L}$) ^{c,d}	76.0 (64.0–89.0)	82.0 (69.2–99.3)	<0.001
Albumin (g/L) ^{c,d}	41.6 (5.0)	39.9 (6.0)	<0.001
Total bilirubin ($\mu\text{mol/L}$) ^{c,d}	14.1 (17.2)	13.5 (10.5)	0.02
Alanine aminotransferase (IU/L) ^d	29.0 (20.0–48.0)	24.0 (17.0–35.0)	<0.001
Positive HBeAg ^{c,d,g}	4,770 (18.2)	156 (10.3)	<0.001
HbA _{1c} (%)	6.4 (3.0)	7.0 (5.1)	<0.001
Time-weighted average HbA _{1c} (%)	12.9 (8.8)	14.3 (9.4)	<0.001
Fasting glucose (mmol/L)	5.7 (1.6)	6.3 (2.3)	<0.001
Triglycerides (mmol/L)	1.2 (0.8)	1.3 (0.9)	<0.001
Total cholesterol (mmol/L)	4.8 (1.0)	4.6 (1.1)	<0.001
LDL-cholesterol (mmol/L)	2.8 (0.8)	2.7 (0.9)	<0.001
HDL-cholesterol (mmol/L)	1.4 (0.4)	1.3 (0.4)	<0.001
Follow-up duration (yr)	3.3 (2.0–6.1)	2.8 (1.5–4.9)	<0.001
Possible reasons for the use of aspirin therapy, n (%)	12,080 (36.2)	1,589 (91.1)	<0.001
Risk factors of cardiovascular disease, n (%) ^h	11,538 (34.6)	1,527 (87.6)	<0.001
Stroke, n (%)	487 (1.5)	338 (19.4)	<0.001
Ischemic heart disease, n (%)	48 (0.1)	278 (15.9)	<0.001
Cardiac dysrhythmias and heart failure, n (%)	977 (2.9)	311 (17.8)	<0.001
Operations on vessels of heart, n (%) ⁱ	6 (0.02)	169 (9.7)	<0.001
Any use of antiviral therapy, n (%) ^{e,j}			
Nucleos(t)ide analogs	33,367 (100.0)	1,744 (100.0)	
Entecavir	28,041 (84.0)	1,508 (86.5)	0.006
Tenofovir disoproxil fumarate	3,402 (10.2)	131 (7.5)	<0.001

Table 1. (continued)

Clinical characteristics	No aspirin use (N = 33,367)	Aspirin use ^a (N = 1,744)	P value ^b
Entecavir + tenofovir disoproxil fumarate	1,924 (5.8)	105 (6.0)	0.636
(Pegylated)-interferon	530 (1.6)	32 (1.8)	0.433
Any use of concomitant drugs, n (%) ^{c,d,e,i}			
Metformin	3,873 (11.6)	467 (26.8)	<0.001
Sulphonylureas	3,924 (11.8)	464 (26.6)	<0.001
Insulin	2,493 (7.5)	348 (20.0)	<0.001
Statins	5,307 (15.9)	1,182 (67.8)	<0.001
ACEIs/ARBs	4,640 (13.9)	771 (44.2)	<0.001
NSAIDs	13,412 (40.2)	879 (50.4)	<0.001
Alanine aminotransferase and follow-up duration were expressed in median (interquartile range), whereas other continuous variables were expressed in mean \pm SD.			
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HBeAg, hepatitis B e antigen; HDL, high-density lipoprotein; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; PS, propensity score.			
^a Aspirin use was defined as a filled prescription for ≥ 90 days, and no use was defined as no aspirin use, during the follow-up period, respectively.			
^b Hypothesis tests compared patients with or without aspirin use at baseline and/or during follow-up. Qualitative and quantitative differences between subgroups were analysed by χ^2 or Fisher exact tests for categorical parameters and the Student <i>t</i> test or Mann-Whitney test for continuous parameters, as appropriate.			
^c Baseline variables were included into imputation model.			
^d Baseline variables and comorbidities associated with aspirin use were balanced in the PS model to minimize “indication bias” and any resultant confounding effects on the HCC and GIB.			
^e All comorbidities and concomitant medications were represented as binary parameters.			
^f Cirrhosis was defined by ICD-9-CM diagnosis codes for cirrhosis.			
^g Percentages were based on nonmissing data.			
^h Hypertension, diabetes mellitus, and dyslipidemia.			
ⁱ All ICD-9-CM procedure code 36.			
^j Any use of medication referred to any use of medication at baseline and/or during follow-up.			

Differences in baseline comorbidities and the usage of medications associated with HCC were observed between the 2 groups (Table 1), and there were potential confounding variables associated with HCC present. Therefore, we developed propensity score (PS), the conditional probability of initiating aspirin, to control for these confounders (16,17). Seventeen important baseline characteristics selected priori were incorporated into the PS model as shown in Table 1. These baseline variables were balanced in the PS model to minimize indication bias and any resultant confounding effects on the HCC and GIB. The balance of covariates by PS was assessed by 2 summary statistics: the absolute standardized mean difference (ASMD) and the Kolmogorov-Smirnov statistic (KS). Both mean and maximum of either ASMD or KS were the 4 stopping rules for assessing the covariate balance between the aspirin group and no aspirin group (i.e., ASMD > 0.2 and/or KS > 0.1 as an indication of imbalance) (18–20). PS matching with a nearest-

neighbor 1:3 matching scheme with the logit of the PS within 0.1 SD was used to balance the clinical characteristics. The relationship between duration of aspirin use and outcomes was evaluated using time-varying aspirin exposures. To assess drug duration, the duration of aspirin for a specific patient was calculated by the sum of the days with filled prescription of aspirin of that user. We counted the days with aspirin prescribed only to achieve high accuracy and updated these data at each new prescription time interval of follow-up.

RESULTS

Patient characteristics

We identified 55,119 CHB patients who received entecavir, tenofovir disoproxil fumarate, and/or tenofovir alafenamide treatment. We excluded 744 patients with coinfections with hepatitis C virus, hepatitis D virus, and HIV; 36 patients with other autoimmune or metabolic liver diseases; 6,464 patients who had incident HCC less than 180 days from baseline date; 241 patients who had liver transplant less than 180 days from baseline; 571 patients who died less than 180 days from baseline; and 122 patients who had history of HCC less than 180 days from baseline. To avoid immortal time bias, 5,683 patients with follow-up of less than 180 days were not included in this study. Furthermore, we excluded 5,555 patients who initiated aspirin earlier than NAs, 187 nonaspirin users who had received other antiplatelet therapy, and 405 aspirin users whose cumulative prescription duration of aspirin was >90 days during follow-up to ensure aspirin efficacy in preventing HCC. In the final analysis, 35,111 patients were included in the study cohorts (Figure 1, 1,744 aspirin group and 33,367 no aspirin group). All study patients were taking aspirin for prevention of cardiovascular and cerebrovascular diseases; no patients took aspirin for HCC prevention. More than 90% of our study participants had high risk of CVD or stroke events while less than 10% of the subjects may had the risk of colorectal cancer and adenomas (Table 1).

The mean age was 53.0 years, and 61.6% were men. One thousand two hundred three (69.0%) male patients belonged to the aspirin group, whereas 20,414 (61.2%) men were in the no aspirin group. Sixty-nine (4.0%) and 1,488 (4.5%) patients

developed HCC at median (IQR) of 2.72 (1.44–4.81) years and 3.23 (1.79–6.01) years in the aspirin group and no aspirin group, respectively. The median (IQR) duration of aspirin prescription was 2.84 (1.57–4.86) years. After a 1:3 PS matching, the total sample size was 6,222 (Table 2, 1,711 aspirin group and 4,511 no aspirin group). The PS-matched cohort was composed of the mean age of 61.9 years and 65.8% men. The median (IQR) of duration of aspirin prescription was changed to 2.57 (1.25–4.62) years.

Hepatocellular carcinoma

In the univariate analysis, the 5-year cumulative incidence of HCC was 3.33% (95% CI 2.48–4.17) in the aspirin group and 3.52% (95% CI 3.32–3.72) in the no aspirin group (difference: –0.2%, 95% CI –0.45% to 0.05%; $P = 0.695$) (Table 3 and Figure 2). In the multivariable model, the aspirin group had a 40% lower risk of HCC than the no aspirin group after adjusting all covariates (adjusted multivariable model subhazard ratio [sHR], 0.60, 95% CI 0.46–0.78; $P < 0.001$) (see Supplementary Table 3, Supplementary Digital Content 3, <http://links.lww.com/CTG/A537>). The results were similar after PS matching for the 2 cohorts (PS-matched sHR, 0.66, 95% CI 0.49–0.87; $P = 0.004$).

Duration of aspirin use in risk of HCC

An inverse relationship between duration of aspirin and the risk of HCC was observed. The duration-dependent association was significant with the use of aspirin longer than 3 months (adjusted sHR from 3 months up to 2 years, 0.65, 95% CI 0.47–0.92) (Table 4). The longer the duration of aspirin had been initiated, the lower the risk of HCC found. The risk of HCC in groups of 2- to 5-year aspirin use and more than 5-year aspirin use were 37% (adjusted sHR from 2 years up to 5 years, 0.63, 95% CI 0.43–0.94) and 59% (adjusted sHR from more than 5 years, 0.41, 95% CI 0.18–0.91) lower than that of the no aspirin group.

Safety of aspirin user in CHB patient: incident GIB

In the univariate analysis, the 5-year cumulative incidence of GIB was 1.78% (95% CI 1.14–2.41) among the aspirin group

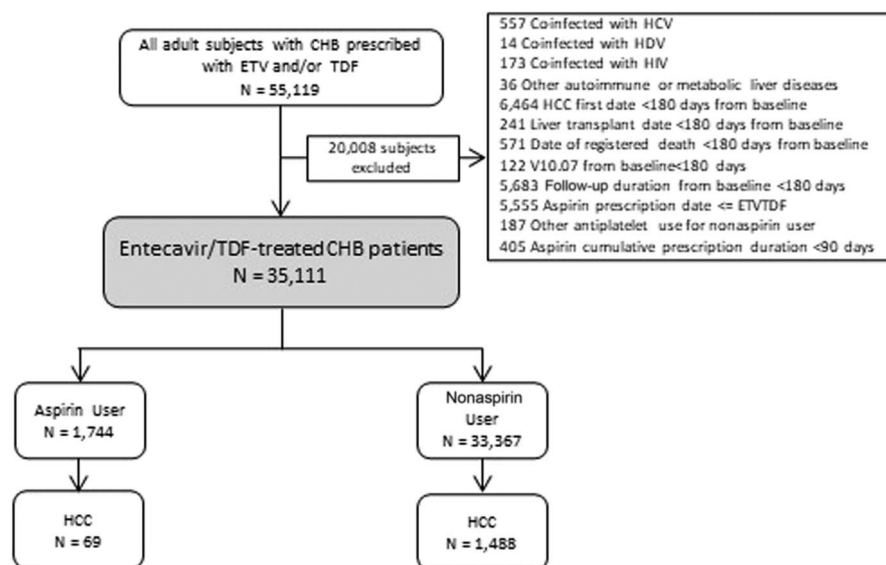


Figure 1. Selection of patients with chronic hepatitis B (CHB) prescribed with first-line oral nucleos(t)ide analogs (ETV and/or TDF). ETV, entecavir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; TDF, tenofovir disoproxil fumarate.

Table 2. Comparison of baseline characteristics before and after propensity score weighting (first imputation)

Clinical characteristics	Unadjusted			PS-matched		
	Aspirin use	Nonaspirin use	ASMD	Aspirin use (N = 1,711)	Nonaspirin use (N = 4,511)	ASMD
Age (yr)	62.2 (10.8)	52.5 (12.5)	0.9	62.1 (10.8)	61.8 (10.5)	0.03
Male sex	1,203 (69.0)	20,414 (61.2)	0.17	1,175 (68.7)	2,918 (64.7)	0.08
Cirrhosis	197 (11.3)	2,177 (6.5)	0.15	189 (11.0)	442 (9.8)	0.04
Hypertension	1,105 (63.4)	7,410 (22.2)	0.85	1,073 (62.7)	2,753 (61.0)	0.04
Renal replacement therapy	58 (3.3)	132 (0.4)		47 (2.7)	64 (1.4)	0.10
Diabetes	662 (38.0)	5,729 (17.2)	0.43	641 (37.5)	1,857 (41.2)	0.09
Platelet ($\times 10^9/L$)	191.2 (92.4)	191.5 (69.9)	0	189.0 (79.4)	188.2 (73.9)	0.01
Creatinine ($\mu\text{mol/L}$)	118.2 (158.3)	80.7 (49.0)	0.24	81.8 (69.0–98.0)	81.0 (68.0–96.0)	0.08
Albumin (g/L)	39.9 (6.0)	41.6 (5.0)	0.28	40.1 (5.9)	40.5 (5.6)	0.09
Total bilirubin ($\mu\text{mol/L}$)	13.5 (10.5)	14.1 (17.2)	0.06	13.6 (10.5)	13.5 (11.9)	0.01
Alanine aminotransferase (IU/L)	24.0 (17.0–35.0)	29.0 (20.0–48.0)	0.45	24.0 (17.0–35.0)	25.0 (18.0–36.0)	0.06
Positive HBeAg	156 (10.3)	4,770 (18.2)	0.22	151 (10.1)	399 (10.8)	0.01
HbA _{1c} (%)	7.0 (5.1)	6.4 (3.0)		7.0 (5.1)	6.8 (3.8)	
Time-weighted average HbA _{1c} (%)	14.3 (9.4)	12.9 (8.8)		14.3 (9.4)	13.8 (9.5)	
Fasting glucose (mmol/L)	6.3 (2.3)	5.7 (1.6)		6.3 (2.3)	6.2 (1.9)	
Triglycerides (mmol/L)	1.3 (0.9)	1.2 (0.8)		1.3 (0.9)	1.3 (0.8)	
Total cholesterol (mmol/L)	4.6 (1.1)	4.8 (1.0)		4.6 (1.1)	4.7 (1.1)	
LDL-cholesterol (mmol/L)	2.7 (0.9)	2.8 (0.8)		2.7 (0.9)	2.8 (0.9)	
HDL-cholesterol (mmol/L)	1.3 (0.4)	1.4 (0.4)		1.3 (0.4)	1.4 (0.4)	
Follow-up duration (yr)	2.8 (1.5–4.9)	3.3 (2.0–6.1)		2.82 (1.5–5.0)	3.1 (1.5–5.3)	
Any use of antiviral therapy						
Nucleos(t)ide analogs	1,744 (100.0)	33,367 (100.0)		1,711 (100.0)	4,511 (100.0)	
ETV	1,508 (86.5)	28,041 (84.0)		1,477 (86.3)	4,032 (89.4)	
TDF	131 (7.5)	3,402 (10.2)		130 (7.6)	303 (6.7)	
ETV + TDF	105 (6.0)	1,924 (5.8)		104 (6.1)	176 (3.9)	
(Pegylated)-interferon	32 (1.8)	530 (1.6)		32 (1.9)	29 (0.6)	
Any use of concomitant drugs						
Metformin	467 (26.8)	3,873 (11.6)	0.34	454 (26.5)	1,369 (30.3)	0.09
Sulphonylureas	464 (26.6)	3,924 (11.8)	0.34	448 (26.2)	1,324 (29.4)	0.07
Insulin	348 (20.0)	2,493 (7.5)	0.31	330 (19.3)	804 (17.8)	0.02
Statins	1,182 (67.8)	5,307 (15.9)	1.11	1,153 (67.4)	3,061 (67.9)	0.01
ACEIs/ARBs	771 (44.2)	4,640 (13.9)	0.61	741 (43.3)	1,930 (42.8)	0.02
NSAIDs	879 (50.4)	13,412 (40.2)	0.2	860 (50.3)	2,240 (49.7)	0.05

Data are shown as mean (SD) or median (interquartile range) or n (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASMD, absolute standardized mean difference; ETV, entecavir; HBeAg, hepatitis B e antigen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; PS, propensity score; TDF, tenofovir disoproxil fumarate.

and 0.75% (95% CI 0.66–0.85) among the no aspirin group (difference: 1.03%, 95% CI 0.89%–1.43%; $P < 0.001$) (Table 3 and Figure 2). The risk of GIB was not significant in the aspirin group after adjusting all covariates (adjusted multivariable model sHR, 1.11, 95% CI 0.87–1.42; $P = 0.391$) (see Supplementary Table 4, Supplementary Digital Content 4, <http://links.lww.com/CTG/A538>). The results were similar after PS-matching analysis (PS-matched sHR, 1.41, 95% CI 0.96–2.08; $P = 0.082$).

Duration of aspirin use in risk of GIB

In general, there was a higher risk of GIB in the aspirin group (adjusted sHR ranged from 0.79 to 1.73) (Table 4). The risk was significantly higher with use of aspirin from 3 months up to 2 years' use than no use (adjusted sHR from 3 months up to 2 years, 1.73, 95% CI 1.07–2.79; $P = 0.026$). However, the risk of GIB started declining with the longer use of aspirin. The adjusted sHR (from 2 years up to 5 years) was 1.19 (95% CI 0.60–2.35; $P = 0.624$) decreased to 0.79 (more than 5 years, 95% CI 0.19–3.21; $P = 0.737$).

Table 3. Effect of aspirin use on risk of incident hepatocellular carcinoma (HCC) and gastrointestinal bleeding (GIB).

Event and treatment group	No. with event/total no.	5-yr cumulative incidence	Hazard ratio (95% confidence interval)		
			Unadjusted	Adjusted (multivariable model)	Propensity score-matched
Incident HCC					
No aspirin use	1,488/33,367	3.33%		1 (reference)	
Aspirin use	69/1,744	3.52%	1.04 (0.80–1.36), <i>P</i> = 0.763	0.60 (0.46–0.78), <i>P</i> < 0.001	0.66 (0.49–0.87), <i>P</i> = 0.004
Absolute risk difference (95%)		–0.2% (–0.45% to 0.05%)			
GIB					
No aspirin use	313/32,763	0.75%		1 (reference)	
Aspirin use	32/1,684	1.78%	1.13 (0.89–1.43), <i>P</i> = 0.331	1.11 (0.87–1.42), <i>P</i> = 0.391	1.41 (0.96–2.08), <i>P</i> = 0.082
Absolute risk difference (95%)		1.03% (0.88% to 1.18%)			

DISCUSSION

We report the chemoprophylactic effect of aspirin on HCC in NA-treated CHB patients in this territorywide, retrospective cohort study. Aspirin use for 5 years or longer was associated with as much as a 40% risk reduction of HCC. A duration-dependent association was significant with the use of aspirin longer than 3 months, which provided at least 35% risk reduction of HCC. In other words, the longer the duration of aspirin had been initiated, the lower the risk of HCC found. The risk of GIB was not significant in long-term aspirin users for 5 years or more; instead, the risk was significantly higher in short-term aspirin users for 3 months to 2 years compared with nonusers.

There has been evolving evidence supporting aspirin to reduce HCC risk in NA-treated CHB patients. Continuing aspirin therapy was recommended by the American Heart Association/American College of Cardiology and American Stroke Association practice guidelines. Therefore, we anticipated that most of our study participants were regular aspirin users (see Supplementary Table 5, Supplementary Digital Content 5, <http://links.lww.com/CTG/A539>). The high medication possession ratio (the duration of aspirin divided by the duration of follow-up) reflected that a majority of aspirin users in this cohort had their therapy on a regular basis (see Supplementary Table 4, Supplementary Digital Content 4, <http://links.lww.com/CTG/A538>). Our PS-matched cohort had shown a 34% risk reduction of HCC, similar to another prospective US cohort study which indicated that regular aspirin use was associated with significantly lower HCC risk compared with non-regular use (multivariable HR 0.51, 95% CI 0.34–0.77) (8). A Taiwanese nationwide cohort study also illustrated daily aspirin therapy had a reduced incidence of HCC in patients with CHB, regardless of whether their antiviral treatment has ever initiated (21). In addition, the effectiveness of aspirin in HCC prevention was confirmed by a recent meta-analysis which was composed of 8 studies with 2,604,319 participants (HR 0.59, 95% CI 0.47–0.75) (22). Furthermore, the prolonged latency effect of aspirin is demonstrated in our study. HCC risk in the aspirin group, with more than 5 years' use, was 59% lower than the no aspirin group. A nationwide Swedish research study reported a similar finding, in which aspirin use more than 5 years would halve the risk of HCC

(multivariable HR 0.57, 95% CI 0.42–0.70) (8). The chemoprophylactic effect of long-term aspirin use on HCC was also verified by another Chinese cohort (10); the risk of developing HCC was reduced by 51% among aspirin users compared with nonusers in mean aspirin duration of 7.7 years (relative risk 0.49).

Several preclinical studies support the function of aspirin in the prevention of HCC by diminishing immune-mediated necroinflammatory reactions, the severity of liver fibrosis or the stage of HCC (11). Inflammation-related cancers such as HCC overexpress the proinflammatory cyclooxygenase-2 (COX-2) enzyme which activates profibrotic and proliferative signaling cascades. Aspirin facilitates selective COX-2 inhibition, which reduces liver fibrosis, portal hypertension, and proliferation of liver cancer cells. All these mechanistic effects contribute to the chemoprophylactic effect of aspirin for HCC (8,23).

GI safety is an imperative concern in long-term antiplatelet therapy. GIB or upper GI upset is mainly contributed by COX-2 inhibition, which protects the delicate lining of the stomach (24,25) and thus makes aspirin as an important risk factor for GIB. In this study, aspirin was not associated with risk of GIB in a 5-year follow-up with adjustment of nonsteroidal anti-inflammatory drug use. Comparable cohorts in Taiwan also reported that GIB events were not significant among the aspirin users as monotherapy. Interestingly, aspirin use for longer duration was as not related to corresponding higher risk of GIB than no aspirin use. The counterintuitive findings were also reported by Simon et al. (8) and Huang et al. (26). Huang et al. concluded that risk of GIB was strongly related to the daily dose rather than duration of aspirin use, such that increasing duration of use did not confer a greater risk of bleeding after adjusting all confounding variables. It was postulated that long-term aspirin use is associated with mucosal adaptations that protect against bleeding events (27). Long-term aspirin use may result in enhancing mucosal expression of nitric oxide synthase and upregulating mucosal cell growth, and thus, a smaller risk estimate is expected (26). Although the mentioned findings are encouraging, practitioners should still be aware of the negative consequence of assigning short-term aspirin therapy as it has significant relationship with GIB risk (Adjusted sHR from 3 months up to 2 years, 1.73, 95% CI 1.07–2.79).

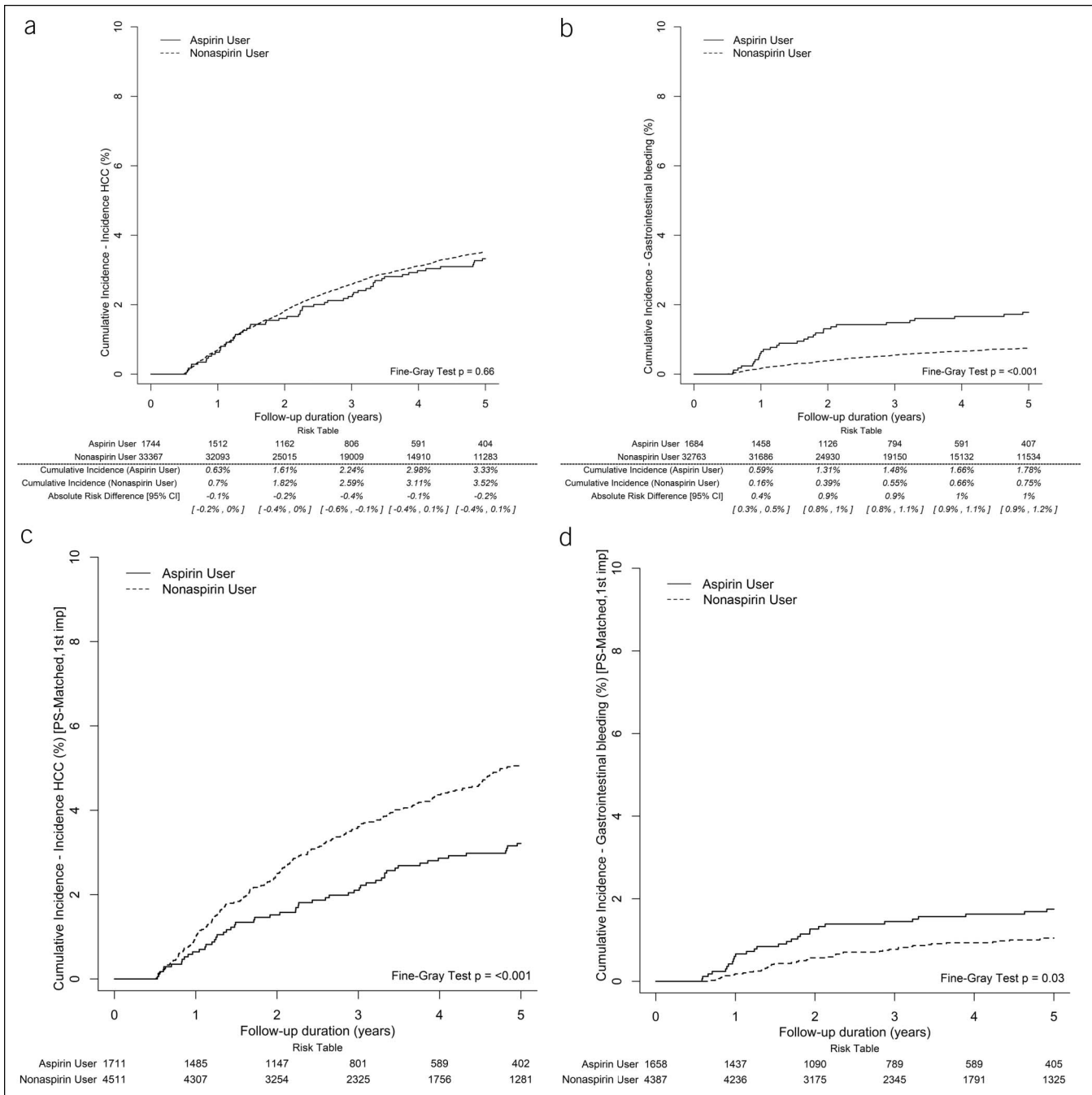


Figure 2. Cumulative incidence of events in the aspirin group vs no aspirin group: (a) HCC (unadjusted), (b) GIB (unadjusted), (c) HCC (PS-adjusted), and (d) GIB (PS-adjusted). CI, confidence interval; GIB, gastrointestinal bleeding; HCC, hepatocellular carcinoma; PS, propensity score.

Aspirin therapy primarily as chemoprophylaxis in CHB patients is not yet a common practice in Hong Kong, which makes the current study an advantage (10). Owing to the fact that most of alike studies were mainly conducted in Western countries, for instance, the United States, those researches would often have difficulty in defining prescription duration of aspirin. Aspirin is an over-the-counter medication that can be easily bought in pharmacies or convenience stores outside the hospital settings thus some of the cohort studies may only able to classify subjects with no regular use of aspirin as the control group (16). As a

result, the effectiveness of aspirin in preventing HCC was not clearly shown in western cohorts. Moreover, our study has the strength of huge sample size of a well-characterized NA-treated CHB patients from this territorywide database, which have led to high statistical power and robust estimators in view of large sample size, together with robust, well-validated diagnosis and procedures coding. Data from real-life cohorts represent a wider spectrum of patients than those in randomized controlled trials, which increases the applicability of our findings to routine clinical practice.

Table 4. Effect of duration of aspirin use on risk of hepatocellular carcinoma (HCC) and gastrointestinal bleeding (GIB).

Duration of aspirin	Hazard ratio (95% confidence interval)	P
Incident HCC		
0 to <3 mo	1 (reference)	
3 mo to <2 yr	0.65 (0.47–0.92)	0.014
2 yr to <5 yr	0.63 (0.43–0.94)	0.022
≥5 yr	0.41 (0.18–0.91)	0.03
GIB		
0 to <3 mo	1 (reference)	
3 mo to <2 yr	1.73 (1.07–2.79)	0.026
2 yr to <5 yr	1.19 (0.60–2.35)	0.624
≥5 yr	0.79 (0.19–3.21)	0.737

We acknowledge several limitations to our study. First, missing data or incomplete data sets would lead to statistical power reduction, biased estimations, and invalid conclusions. Multiple imputation was introduced to rectify our analysis. Low imputation error and small prediction differences between imputation models were proven. We hoped that multiple imputation could narrow the uncertainty about missing values and hence the unnecessary variability. Second, the measured and unmeasured confounding factors may distort the observed association between aspirin therapy and risk of HCC or GIB. PS matching was adopted to adjust the potential confounders, such as laboratory parameters and medications in the multivariable model. The reasons for patients undergoing aspirin therapy depended on their comorbidities such as the risk of cardiovascular disease. Therefore, this study has tried to match patients with similar comorbidities such as diabetes, hypertension, and statin use (the indication of dyslipidemia) in the PS-matched cohort. As a result, this cofounder should have had less influence on the incidence of HCC. Third, the retrospective nature of this study had posed a primitive difficulty in tracing each patients' medical records or some patients might be lost to follow-up. Some patients might have treatments provided by private hospitals, and some patients may have emigrated. The true beneficial impact of aspirin on reducing risk of HCC might have been underestimated. Fourth, HBV DNA was not included in any part of this analysis because of the large missing proportion. The strong association between HBV DNA viral load and progression of HCC is often reported. Therefore, the number of cirrhosis cases may be underreported. Excluding HBV DNA is for the sake of imputation quality and accuracy for further regression models and PS matching.

In conclusion, this territorywide, retrospective cohort study showed that aspirin use is associated with a lower risk of HCC in a duration-dependent manner in NA-treated CHB patients without a significant increase in the risk of GI adverse effects. This study has provided important evidence for the practice guidelines to review the chemoprophylactic strategy in CHB patients, particularly those are at risk of HCC. Aspirin therapy may provide additional benefit to NA treatment to further reduce HCC risk.

CONFLICTS OF INTEREST

Guarantor of the article: Grace Lai-Hung Wong, MD.

Specific author contributions: V.W.-K.H., T.C.-F.Y, Y.-K.T., and G.L.-H.W.: were responsible for the acquisition and analysis of data and had full take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for the study concept and design for the interpretation of data, drafting, and critical revision of the article for important intellectual content.

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Potential competing interests: V.W.-S. Wong has served as an advisory committee member for AbbVie, Allergan, Echosens, Gilead Sciences, Janssen, Perspectum Diagnostics, Pfizer, and Terns and a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences and Merck. T.C.-F. Yip has served as a speaker and an advisory committee member for Gilead Sciences. H.L.-Y. Chan has served as an advisory committee member for AbbVie, Aptorum, Altimmune, Arbutus, ContraVir, Intellia, Janssen, Gilead, MedImmune, Roche, Vir Biotechnology, GRAIL, and Vaccitech and as a speaker for AbbVie, Gilead, and Roche. G.C.-Y. Lui has served as an advisory committee member for Gilead, Merck, and GSK, speaker for Merck and Gilead, and received research grant from Gilead, Merck, and GSK. G.L.-H. Wong has served as an advisory committee member for Gilead Sciences and Janssen, as a speaker for Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche and received research grant from Gilead Sciences. The other authors declare that they have no competing interests.

Study Highlights

WHAT IS KNOWN

- ✓ Aspirin therapy may provide additional chemopreventive benefit on top of treatment to further reduce hepatocellular carcinoma risk.

WHAT IS NEW HERE

- ✓ Long-term aspirin use is associated with a lower risk of hepatocellular carcinoma in a duration-dependent manner in nucleos(t)ide analog-treated chronic hepatitis B patients, without a significant increase in the risk of gastrointestinal (GI) adverse effects
- ✓ Patients who took shorter duration of aspirin for ≤2 years had significantly higher risk of GI bleeding than those not receiving aspirin. The risk of GI bleeding started declining with the longer use of aspirin and becoming insignificant for ≥5 years' use.

TRANSLATIONAL IMPACT

- ✓ Long-term aspirin use is associated with a lower risk of HCC in a duration-dependent manner in NA-treated CHB patients without a significant increase in the risk of gastrointestinal adverse effects.

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