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Aspirin Use and Risk of HCC and Gastrointestinal Bleeding in Patients With HBV-Related Cirrhosis: A Landmark Analysis

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Keywords: aspirin | chronic hepatitis B | cirrhosis | gastrointestinal bleeding | hepatocellular carcinoma

ABSTRACT

Background and Aims: The use of aspirin in hepatocellular carcinoma (HCC) prevention and the risk of gastrointestinal (GI) bleeding is still uncertain in patients with hepatitis B virus (HBV)-related cirrhosis. We investigated the association between aspirin use and the risks of HCC and GI bleeding in patients with HBV-related cirrhosis.

Methods: We conducted a 3-year landmark analysis using nationwide cohort data from the National Health Insurance Service of South Korea. Patients diagnosed with compensated HBV-related cirrhosis in 2005–2017 were included. Patients who were prescribed aspirin for at least 90 days consecutively during the 3-year exposure period were classified as the aspirin-treated group. The risks of HCC and GI bleeding were estimated in a cohort matched by propensity scores.

Results: During a median of 7.6 years of follow-up, the 10-year cumulative incidence of HCC was 41.8% among aspirin users ($n = 608$) and 46.5% among nonusers ($n = 2432$) ($p = 0.033$). The aspirin-treated group showed a significantly lower risk of HCC than the untreated group (adjusted hazard ratio [aHR] = 0.84, 95% confidence interval [CI] = 0.73–0.96; $p = 0.013$). The 10-year cumulative incidence of GI bleeding was 29.5% among aspirin users and 24.0% among nonusers ($p = 0.016$). The aspirin-treated group showed a significantly higher risk of GI bleeding than the untreated group (aHR = 1.20, 95% CI = 1.02–1.42; $p = 0.029$).

Conclusions: In patients with HBV-related cirrhosis, the aspirin-treated group showed a significantly lower risk of HCC than the untreated group, whereas the risk of GI bleeding was significantly higher in the aspirin-treated group.

Abbreviations: AVT, antiviral therapy; aHR, adjusted hazard ratio; CHB, chronic hepatitis B; CI, confidence interval; COX-2, cyclooxygenase-2; DDD, defined daily dose; GI, gastrointestinal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; NHIS, National Health Insurance Service; PSM, propensity score matching.

1 | Introduction

The clinical outcomes of patients with chronic hepatitis B (CHB) have improved in the era of potent nucleos(t)ide analogue (NUC) therapy [1]. However, the risk of hepatocellular carcinoma (HCC) has remained, especially among patients with advanced fibrosis or cirrhosis [2–4]. Thus, HCC-preventive strategies among patients with hepatitis B virus (HBV)-related cirrhosis are crucial [5]. Particular attention has been given in recent years to the anti-cancer potential of aspirin [6]. Regarding the risk of HCC, low-dose aspirin also had a preventive effect in animal models [7, 8]. These findings have been supported by much epidemiological evidence [9].

However, results are controversial about the preventive effect of aspirin for HCC development among patients with HBV-related cirrhosis. Large nationwide studies from Sweden [10] and Korea [11] reported that the anti-HCC effect of aspirin remained among patients with HBV-related cirrhosis. In contrast, a recent stratified analysis from Korea [12] reported that cirrhosis status had a significant effect on the association between aspirin use and the risk of HCC, and the anti-HCC effect was not confirmed among patients with HBV-related cirrhosis.

Given that none of these studies was specifically designed to investigate the preventive effects of aspirin among patients with HBV-related cirrhosis, and the issue of immortal time bias has not been fully addressed, additional data are still required to characterize the potential benefits of aspirin more comprehensively within the spectrum of HBV-related cirrhosis. In addition, the risk of gastrointestinal (GI) bleeding in patients with HBV-related cirrhosis who use aspirin has not yet been clarified.

Accordingly, we investigated the association between aspirin use and the risk of HCC and GI bleeding in patients with HBV-related cirrhosis using a nationwide cohort.

2 | Methods

2.1 | Data Source

Data obtained from the National Health Insurance Service (NHIS) database in Korea, comprising health care data, including diagnoses, procedures, prescriptions, and health examination data, was used in this nationwide cohort study. As outlined in previous studies [13], the database has proven reliability and validity. This study was approved by the Institutional Review Board of Yonsei University College of Medicine (no. 4-2023-0461), which waived the requirement for written informed consent because the NHIS database was built anonymously under strict confidentiality guidelines.

2.2 | Study Population

We identified patients with HBV-related cirrhosis based on International Classification of Diseases, 10th Revision (ICD-10) codes (Table S1) between 2005 and 2017. The exclusion criteria were as follows: (1) coinfection with hepatitis C virus; (2) coinfection with HIV; (3) prior aspirin prescription; (4) prior diagnosis of HCC; (5) prior liver transplantation; (6) prior GI bleeding; (7) decompensated cirrhosis.

To avoid reverse causation and immortal-time bias, we applied a landmark analysis with a 3-year exposure period from the cohort entry date, defined as the date of initial HBV-related cirrhosis diagnosis. The index date was set as 3 years after the cohort entry date. During a 3-year exposure period, 6270 patients were excluded because of death, undergoing liver transplantation, HCC development, or a follow-up period < 3 years. The aspirin users were defined as patients prescribed aspirin 100 mg [14] for at least 90 days consecutively within the 3-year exposure period. Aspirin nonusers were defined as patients without any prescription throughout the entire study period; those who initiated aspirin after the exposure period were further excluded (Figure S1).

A total of 608 aspirin users were randomly matched in a 1:4 ratio, with aspirin nonusers using propensity scores comprising baseline characteristics (age, sex, type 2 diabetes, hypertension, dyslipidemia), and the use of potentially chemopreventive drugs with more than 30 cumulative defined daily doses (DDDs) (anti-HBV therapy, statin, and metformin) during follow-up. Diagnostic codes and detailed definitions used in the present study are provided in Table S1. The cumulative DDD was defined according to the Anatomic Therapeutic Chemical classification system and the 2020 DDD index [15].

2.3 | Outcomes

The primary outcomes were HCC development and the first occurrence of GI bleeding. Development of HCC was defined by ICD-10 code C22.0. GI bleeding was defined by the corresponding ICD-10 codes (Table S1). The secondary outcomes were all-cause and liver-related mortality. Information from death certificates, including the date and cause of death, was obtained from the Statistics Korea database, merged into the data set, and used for the analyses of all-cause and liver-related mortality.

2.4 | Statistical Analysis

A propensity score matching (PSM) analysis was performed to reduce potential confounding between the two groups. Propensity scores were calculated through a logistic regression model to estimate the probabilities of assigning a patient to the treated group, including the following variables: age, sex, hypertension, type 2 diabetes, dyslipidemia, use of anti-HBV therapy, statin, and metformin usage.

The follow-up of the study patients began from the index date and lasted until the date of HCC development, GI bleeding, any competing event, or the end of the study period (December 31, 2017), whichever came first. The Fine-Gray competing risk regression analysis was used to estimate adjusted hazard ratios (aHRs) and corresponding 95% confidence intervals (CIs) of study outcomes (HCC, GI bleeding, all-cause, and liver-related

mortality). Competing risk was accounted for as follows: overall death as a competing risk for analyses of HCC and GI bleeding; death from another cause as a competing risk for liver-related mortality.

All statistical analyses were performed as two-sided tests, and p values <0.05 were considered statistically significant. The data collection and statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3 | Results

3.1 | Study Population

The median follow-up duration of the enrolled patients was 7.6 years (interquartile range, 3.8–11.5). In the aspirin user group, the median duration of aspirin use was 361 days (interquartile range, 180–664). The patients' baseline characteristics are presented in Table 1. Aspirin users tended to be older, had more hypertension, type 2 diabetes, or dyslipidemia, and received anti-HBV therapy, statin, or metformin (all $p<0.05$). After the PSM adjustment, all covariates were well balanced (i.e., standardized mean differences were <0.1).

3.2 | Risk of HCC Development

During the follow-up period, 4339 patients developed HCC, including 219 in the aspirin user group and 4120 in the nonuser group. Aspirin users had a 16% lower risk of HCC than nonusers after multivariable adjustment (aHR, 0.84; 95% CI, 0.73–0.96; $p=0.013$). The results were similar in the PS-matched cohort where aspirin users had a 16% lower risk of HCC than nonusers after multivariable adjustment (aHR, 0.85; 95% CI, 0.74–0.99; $p=0.036$) (Table 2). In the PS-matched cohort, the 10-year cumulative incidence of HCC was 41.8% (95% CI, 37.3–46.3) among aspirin users and 46.5% (95% CI, 43.9–48.9) among nonusers. The cumulative incidence of HCC was significantly lower in the aspirin users than in the nonusers ($p=0.033$, by Gray's test; Figure 1).

3.3 | Risk of GI Bleeding

GI bleeding occurred in 2136 patients during follow-up: 157 in the aspirin user group and 1979 in the nonuser group. Aspirin users had a 20% higher risk of HCC than nonusers after multivariable adjustment (aHR, 1.20; 95% CI, 1.02–1.42; $p=0.029$). The results were similar in the PS-matched cohort where aspirin users had a 26% higher risk of HCC than nonusers after multivariable adjustment (aHR, 1.26; 95% CI, 1.05–1.51; $p=0.013$) (Table 3). In the PS-matched cohort, the 10-year cumulative incidence of GI bleeding was 29.5% (95% CI, 25.4–33.7) among aspirin users and 24.0% (95% CI, 21.9–26.2) among nonusers. The cumulative incidence of GI bleeding was significantly higher in the aspirin users than in the nonusers ($p=0.016$, by Gray's test; Figure 2).

3.4 | Risk of All-Cause and Liver-Related Mortality

In the PS-matched cohort, although aspirin users showed slightly lower risk of all-cause and liver-related mortality compared to nonusers, the differences did not reach statistical significance (aHR, 0.86; 95% CI, 0.69–1.07; $p=0.168$ for all-cause mortality; aHR, 0.87; 95% CI, 0.63–1.21; $p=0.416$ for liver-related mortality) (Table S2). The cumulative incidence of all-cause (Figure S2A) and liver-related mortality (Figure S2B) also did not differ significantly between the aspirin users and nonusers ($p=0.505$ for all-cause mortality; $p=0.550$ for liver-related mortality by Gray's test).

TABLE 1 | Baseline characteristics of the study participants according to aspirin-use status before and after propensity score matching.

	Before matching				After MATCHING		
Variables	**Aspirin use ($n=608$)**	**No aspirin use ($n=11\,608$)**	***p***	**SMD**	**Aspirin use ($n=608$)**	**No Aspirin use ($n=2432$)**	**SMD**
Demographic variables							
Age, years	55.7 ± 9.7	49.7 ± 10.6	<0.001	0.591	55.7 ± 9.7	55.5 ± 9.3	0.027
Male	443 (72.9)	8112 (69.5)	0.075	0.075	443 (72.9)	1747 (71.8)	0.023
Hypertension	356 (58.6)	3865 (33.1)	<0.001	0.528	356 (58.6)	1457 (59.9)	0.028
Type2 diabetes	424 (69.7)	5931 (50.8)	<0.001	0.395	424 (69.7)	1699 (69.9)	0.003
Dyslipidemia	355 (58.4)	6114 (52.4)	0.004	0.122	355 (58.4)	1400 (57.6)	0.017
Drug use							
Anti-hepatitis B virus therapy	121 (19.9)	3717 (31.8)	<0.001	0.275	121 (19.9)	452 (18.6)	0.030
Statin	100 (16.5)	1143 (9.8)	<0.001	0.198	100 (16.5)	372 (15.3)	0.034
Metformin	161 (26.5)	1657 (14.2)	<0.001	0.309	161 (26.5)	628 (25.8)	0.017

Note: Data are presented as mean ± SD or number (%). Antiviral therapy includes lamivudine, adefovir, telbivudine, clevudine, entecavir, or tenofovir. Antiviral therapy, Statin, and Metformin use was defined as a filled prescription for more than 30 cumulative defined daily doses. SMD, standardized mean difference.

TABLE 2 | Risk of hepatocellular carcinoma according to the aspirin-use status (before and after PS matching).

	N	Event	Person-years	Incidence-rate[a]	Hazard ratio (95% confidence interval)	
					Unadjusted	Multivariable-adjusted[b]
Before PS matching						
No aspirin use	11 680	4120	61547.6	66.9	1 (reference)	1 (reference)
Aspirin use	608	219	3607.9	60.7	0.91 (0.79–1.04)	0.84 (0.73–0.96)
p value					0.150	0.013
After PS matching						
No aspirin use	2432	878	12012.6	73.1	1 (reference)	1 (reference)
Aspirin use	608	219	3607.9	60.7	0.86 (0.74–0.99)	0.85 (0.74–0.99)
p value					0.039	0.036

Abbreviation: PS, propensity score.
[a]Incidence per 1000 person-years.
[b]Adjusted for age, sex, hypertension, type 2 diabetes, dyslipidemia, use of anti-hepatitis B virus therapy, use of statin, use of metformin.

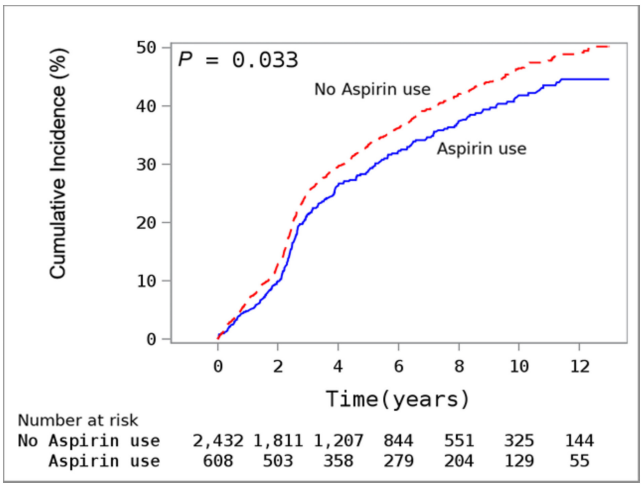

FIGURE 1 | Cumulative incidences of HCC according to the aspirin-use status. Gray's test was used to compare cumulative incidences between aspirin users and nonusers, accounting for death from any cause as a competing risk.

3.5 | Duration of Aspirin Use and Risk of HCC and GI Bleeding

The risk of HCC was not significantly different between aspirin nonusers and those who used aspirin for 3 months to 1 year (aHR, 1.19; 95% CI, 0.88–1.60) or for 1 to 3 years (aHR, 1.04; 95% CI, 0.81–1.34). In contrast, patients who continued aspirin therapy for more than 3 years had a significantly reduced risk of HCC compared with nonusers (aHR, 0.68; 95% CI, 0.56–0.82). No significant association between aspirin duration and the risk of GI bleeding was observed (Table 4).

3.6 | Sensitivity Analysis

In the sensitivity analysis, aspirin nonusers were more broadly defined to include patients who were never prescribed aspirin or prescribed for fewer than 90 days during the exposure period [10]. Using this definition, the results remained consistent with the main analysis, showing that aspirin was associated with a reduced risk of HCC and an increased risk of GI bleeding (Tables S3 and S4).

To account for potential bias introduced by aspirin discontinuation during follow-up, we performed sensitivity analyses stratified by aspirin continuation versus discontinuation at 1-year and 3-year cutoffs (Table S5). At the 1-year cutoff, discontinuation within 1 year showed no significant association with HCC or GI bleeding, whereas continuation for ≥ 1 year was linked to reduced HCC risk (aHR 0.78, 95% CI 0.67–0.91) but modestly increased GI bleeding risk (aHR 1.24, 95% CI 1.04–1.47). At the 3-year cutoff, HCC risk reduction was evident only with > 3 years of aspirin use (aHR 0.68, 95% CI 0.56–0.82). Notably, GI bleeding risk was elevated with 1–3 years of use (aHR 1.94, 95% CI 1.47–2.55) but not with > 3 years (aHR 0.98, 95% CI 0.79–1.22).

4 | Discussion

Daily low-dose aspirin use was associated with a 16% lower risk of incident HCC in this nationwide population-based study of 12,216 patients with HBV-related cirrhosis. However, the aspirin use was accompanied by a substantially higher incidence of GI bleeding (20% increased risk). In the duration-stratified analysis, a significant reduction in the risk of HCC was observed among patients who continued aspirin for more than 3 years. To minimize potential biases, including immortal time bias and confounding, we applied a landmark analysis along with PSM and multivariable adjustments.

The preventive effect of aspirin was controversial in patients with HBV-related cirrhosis. The large nationwide study from Sweden [10] showed that aspirin use was associated with a significantly lower risk of HCC among patients with chronic viral hepatitis regardless of the presence of cirrhosis. A Taiwanese nationwide cohort study showed no significant association between aspirin use and the risk of HCC in patients with HBV-related cirrhosis [16]. Two nationwide Korean studies using the NHIS Database

TABLE 3 | Risk of gastrointestinal bleeding according to the aspirin-use status (before and after PS matching).

	N	Event	Person-years	Incidence-rate[a]	Hazard ratio (95% confidence interval)	
					Unadjusted	Multivariable-adjusted[b]
Before PS matching						
No aspirin use	11 680	1979	77036.1	25.7	1 (reference)	1 (reference)
Aspirin use	608	157	4149.7	37.8	1.45 (1.24–1.70)	1.20 (1.02–1.42)
p value					< 0.001	0.029
After PS matching						
No aspirin use	2432	455	14784.9	30.8	1 (reference)	1 (reference)
Aspirin use	608	157	4149.7	37.8	1.26 (1.05–1.51)	1.26 (1.05–1.51)
p value					0.013	0.013

Abbreviation: PS, propensity score.
[a]Incidence per 1000 person-years.
[b]Adjusted for age, sex, hypertension, type 2 diabetes, dyslipidemia, use of anti-hepatitis B virus therapy, use of statin, and use of metformin.

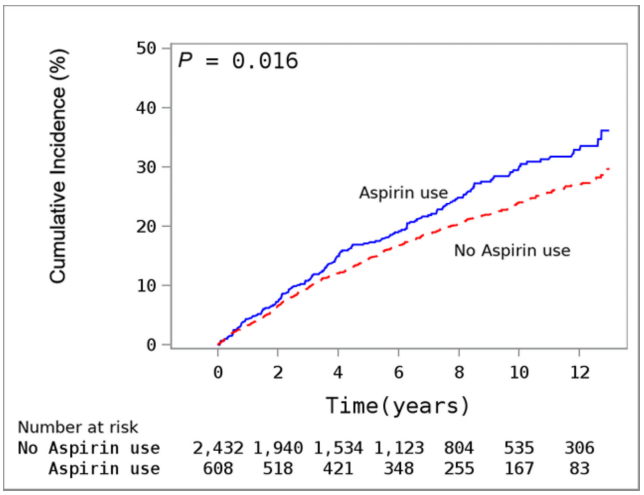

FIGURE 2 | Cumulative incidences of GI bleeding according to the aspirin-use status. Gray's test was used to compare cumulative incidences between aspirin users and nonusers, accounting for death from any cause as a competing risk.

also reported conflicting findings in patients with HBV-related cirrhosis [11, 12]. These discrepancies likely reflect methodological differences. One [11] defined aspirin users as individuals with at least 3 years of use during follow-up and excluded patients with decompensated cirrhosis, thus focusing on a population with compensated disease, whereas the other study [12] classified aspirin users as those with at least 90 consecutive days of use, set the index date at day 180, and included patients with decompensated cirrhosis. Such differences in the definition of aspirin users, cirrhosis classification, and approaches to time-related bias likely contributed to the divergent results.

However, most previous studies were not originally designed to investigate the anti-HCC effect of aspirin specifically in patients with HBV-related cirrhosis. Thus, the effect of aspirin on HBV-related cirrhosis was only analyzed in the subgroup analyses, often without adequately addressing immortal time bias. In addition, many studies included patients with decompensated cirrhosis, who are at a much higher risk of HCC; thus, daily aspirin use for preventing HCC might not be feasible in such a clinical setting. All these limitations make it difficult to derive the clinical implications of aspirin use among patients with HBV-related cirrhosis. In our study, we sought to address these methodological issues by restricting the cohort to patients with compensated cirrhosis and by applying a landmark analysis to minimize time-related bias.

Although potent NUC therapy suppresses HBV replication and inflammation, patients with HBV-related cirrhosis remain at residual risk of HCC due to irreversible fibrosis, vascular remodeling, and non-virological factors [17, 18]. Our findings suggest that aspirin could still contribute to risk reduction in this population, although the magnitude of its effect in clinical practice may be smaller than in NUC-untreated patients. Experimental studies support this potential, showing that aspirin attenuates liver disease progression and hepatocarcinogenesis [19, 20], even in cirrhotic models [21]. Several mechanisms can explain this phenomenon. Aspirin might have an anti-HCC effect by inhibiting the selective cyclooxygenase-2 (COX-2) overexpression associated with diminishing liver fibrosis, portal hypertension, and proliferation of liver cancer cells [22]. In addition, the sustained inhibition of platelet function by low-dose aspirin reduced the number of intrahepatic HBV-specific CD8 T cells that would otherwise trigger the progression to liver fibrosis and the development of HCC [7, 8].

The imperative concern about the long-term use of aspirin among patients with HBV-related cirrhosis is GI bleeding. Cirrhosis is a well-known risk factor for GI bleeding, such as bleeding from portal hypertension-related varices [23, 24] and peptic ulcer bleeding [25] because of the high bleeding tendency related to a lower platelet count and prolonged prothrombin time [26, 27]. In this high-risk population, the potential benefits of aspirin must be balanced against bleeding risk. In our study, aspirin use was associated with a significantly increased risk of newly developed GI bleeding, consistent with a previous meta-analysis showing a 1.7-fold higher risk [28]. In addition, a previous study reported that aspirin use may be associated with an increased risk of major bleeding in patients with cirrhosis than in those without cirrhosis, which suggests the need for cautious use of aspirin in

TABLE 4 | Risk of hepatocellular carcinoma and gastrointestinal bleeding according to the duration of aspirin use.

	Aspirin duration			
	No aspirin	3 mon to 1 year	1 to 3 years	Over 3 years
Hepatocellular carcinoma				
No. with event/total no.	4120/11680	43/96	68/183	108/329
10 year cumulative incidence, %	43.8	52.6	45.8	36.9
Multivariable-adjusted HR (95% CI)[a]	1 (reference)	1.19 (0.88–1.60)	1.04 (0.81–1.34)	0.68 (0.56–0.82)
Gastrointestinal bleeding				
No. with Event/Total No.	1979/11680	20/92	57/180	80/336
10 year cumulative incidence, %	21.2	23.9	37.8	26.6
Multivariable-adjusted HR (95% CI)[a]	1 (reference)	1.02 (0.65–1.61)	1.94 (1.47–2.55)	0.98 (0.79–1.22)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, hypertension, type 2 diabetes, dyslipidemia, use of anti-hepatitis B virus therapy, use of statin, and use of metformin.

patients with cirrhosis [29]. While some studies reported no significant increase, they included patients with prior GI bleeding or decompensated cirrhosis [10, 12]. By excluding such patients, we restricted our analysis to compensated cirrhosis, thereby providing a more reliable estimate of bleeding risk.

Interestingly, aspirin use did not increase the risk of GI bleeding in a duration-dependent manner. The counterintuitive findings were also reported by Huang et al. [28]. In that study, the daily dose of aspirin was associated with the risk of GI bleeding, whereas the duration of aspirin use was not. Long-term aspirin use may be associated with mucosal adaptations by enhancing mucosal expression of nitric oxide synthase and upregulating mucosal cell growth to protect against bleeding events [30]. Thus, aspirin use in patients with HBV-related cirrhosis should be monitored carefully, and the benefits and harms of aspirin use for HCC prevention should be weighed as recommended in practice guidelines [31]. However, it is possible that other confounding factors could not be evaluated in the database, such as the underlying presence of peptic ulcer or varices. Although the effect of aspirin on HCC development is noteworthy, future research is needed to define its potential hazards. Future studies with detailed information associated with the risk of GI bleeding are needed to clearly postulate the risk of GI bleeding in aspirin users with HBV-related cirrhosis.

Our sensitivity analyses showed that the protective effect of aspirin against HCC was limited to patients who continued treatment. Discontinuation within 1 year conferred no benefit, whereas use for ≥ 1 year was associated with reduced HCC risk, with the strongest effect observed after > 3 years of continuous use. This suggests that sustained exposure is required for a chemopreventive effect. However, long-term use also increased the risk of GI bleeding, emphasizing the need to balance potential benefits against bleeding hazards and to individualize decisions in patients with cirrhosis.

Aspirin use was not associated with all-cause and liver-related mortality benefits in our study. It is plausible that the aspirin nonusers may experience HCC-related mortality while aspirin users may die from other causes, such as GI bleeding-related events. Also, aspirin users might be at higher risk of cardiovascular causes. Furthermore, the number of cases was relatively small due to the exclusion of events occurring within the exposure period per the landmark method, which could have caused the loss of statistical power.

The strengths of our study include its inclusion of a large homogeneous robust cohort of HBV-related cirrhosis that enabled a potent analysis. Our results can provide sole evidence of the benefits and harms of long-term aspirin use among patients with HBV-related cirrhosis to guide clinical practice. In addition, with the incorporation of a landmark analysis, we provided an unbiased demonstration of the effect of aspirin use on the risk of HCC by eliminating the immortal time bias, which is often unrecognized in epidemiologic studies of drug effect on disease development, conferring a survival advantage to treated groups [32].

Nevertheless, our study has several limitations. First, as a retrospective cohort study, unmeasured confounding could not be fully eliminated, despite multiple statistical approaches. Second, detailed clinical information on HBV activity could not be obtained from our database. Instead, we adjusted the use of AVT, which could partially reflect the CHB status, as AVT is usually prescribed for patients with active CHB according to the NHIS reimbursement criteria [33]. In addition, clinical and laboratory parameters reflecting advanced fibrosis, such as platelet count or histological fibrosis stage, could not be obtained in our database. As advanced fibrosis is closely linked to the risk of HCC and may influence both treatment allocation and outcomes, the inability to account for these factors may have introduced residual confounding. Furthermore, information on the primary indication for aspirin use was not available, which may limit the interpretation of patient characteristics. Future studies with access to detailed clinical and laboratory data are warranted to validate and extend our findings. Third, the aspirin group was relatively small, reflecting our strict inclusion criteria, which reduced the sample size but strengthened exposure ascertainment and internal validity. Future studies with richer clinical data are needed to confirm and extend these findings.

In conclusion, in a nationwide population of patients with HBV-related cirrhosis, aspirin use was associated with a significantly

lower risk of HCC, whereas the risk of GI bleeding development was significantly higher in the aspirin users than nonusers. Our findings suggest that careful follow-up for monitoring of GI bleeding is needed if aspirin is considered an HCC prevention strategy among patients with HBV-related cirrhosis.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

References

1. C. L. Lin and J. H. Kao, "Global Strategies and Actions to Eliminate HBV Infection," *Clinical and Molecular Hepatology* (2025).

2. G. V. Papatheodoridis, R. Idilman, G. N. Dalekos, et al., "The Risk of Hepatocellular Carcinoma Decreases After the First 5 Years of Entecavir or Tenofovir in Caucasians With Chronic Hepatitis B," *Hepatology* 66 (2017): 1444–1453.

3. M. N. Kim, J. W. Han, J. An, et al., "KASL Clinical Practice Guidelines for Noninvasive Tests to Assess Liver Fibrosis in Chronic Liver Disease," *Clinical and Molecular Hepatology* 30 (2024): S5–s105.

4. L. Y. Mak, "Disease Modifiers and Novel Markers in Hepatitis B Virus-Related Hepatocellular Carcinoma," *Journal of Liver Cancer* 24 (2024): 145–154.

5. M. H. Lee, "Public Health Strategies for Hepatocellular Carcinoma: From Risk Factors to Prevention and Control," *Journal of Liver Cancer* (2025).

6. Y. Cho, B. H. Kim, and J. W. Park, "Preventive Strategy for Nonalcoholic Fatty Liver Disease-Related Hepatocellular Carcinoma," *Clinical and Molecular Hepatology* 29 (2023): S220.

7. G. Sitia, R. Aiolfi, P. Di Lucia, et al., "Antiplatelet Therapy Prevents Hepatocellular Carcinoma and Improves Survival in a Mouse Model of Chronic Hepatitis B," *Proceedings of the National Academy of Sciences of the United States of America* 109 (2012): E2165–E2172.

8. G. Sitia, M. Iannacone, and L. G. Guidotti, "Anti-Platelet Therapy in the Prevention of Hepatitis B Virus-Associated Hepatocellular Carcinoma," *Journal of Hepatology* 59 (2013): 1135–1138.

9. T. G. Simon and A. T. Chan, "Lifestyle and Environmental Approaches for the Primary Prevention of Hepatocellular Carcinoma," *Clinics in Liver Disease* 24 (2020): 549–576.

10. T. G. Simon, A. S. Duberg, S. Aleman, R. T. Chung, A. T. Chan, and J. F. Ludvigsson, "Association of Aspirin With Hepatocellular Carcinoma and Liver-Related Mortality," *New England Journal of Medicine* 382 (2020): 1018–1028.

11. B. Yun, S. H. Ahn, J. H. Yoon, and B. K. Kim, "Clinical Indication of Aspirin Associated With Reduced Risk of Liver Cancer in Chronic Hepatitis B: A Nationwide Cohort Study," *American Journal of Gastroenterology* 117 (2022): 758–768.

12. H. Jang, Y. B. Lee, H. Moon, et al., "Aspirin Use and Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B With or Without Cirrhosis," *Hepatology* 76 (2022): 492–501.

13. S. Cheol Seong, Y. Y. Kim, Y. H. Khang, et al., "Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea," *International Journal of Epidemiology* 46 (2017): 799–800.

14. S. Wang, Y. Yu, P. M. Ryan, et al., "Association of Aspirin Therapy With Risk of Hepatocellular Carcinoma: A Systematic Review and Dose-Response Analysis of Cohort Studies With 2.5 Million Participants," *Pharmacological Research* 151 (2020): 104585.

15. WHO Collaborating Centre for Drug Statistics Methodology, "ATC Index With DDDs," (2020).

16. T. Y. Lee, Y. C. Hsu, H. C. Tseng, et al., "Association of Daily Aspirin Therapy With Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B," *JAMA Internal Medicine* 179 (2019): 633–640.

17. M. Zoncapè and E. A. Tsochatzis, "The Use of Transient Elastography for Predicting Hepatocellular Carcinoma in Chronic Hepatitis B Patients: Editorial on "Risk Assessment of Hepatitis B Virus-Related Hepatocellular Carcinoma Development Using Vibration-Controlled Transient Elastography: Systematic Review and Meta-Analysis"," *Clinical and Molecular Hepatology* 31 (2025): 268–274.

18. R. Huang, D. W. Jun, H. Toyoda, et al., "Impacts of Metabolic Syndrome Diseases on Long-Term Outcomes of Chronic Hepatitis B Patients Treated With Nucleos(t)ide Analogues," *Clinical and Molecular Hepatology* 31 (2025): 1003–1017.

19. E. Ricciotti, K. J. Wangensteen, and G. A. FitzGerald, "Aspirin in Hepatocellular Carcinoma," *Cancer Research* 81 (2021): 3751–3761.

20. M. J. Goh and D. H. Sinn, "Statin and Aspirin for Chemoprevention of Hepatocellular Carcinoma: Time to Use or Wait Further?," *Clinical and Molecular Hepatology* 28 (2022): 380–395.

21. N. Assy, O. Hussein, A. Khalil, et al., "The Beneficial Effect of Aspirin and Enoxaparin on Fibrosis Progression and Regenerative Activity in a Rat Model of Cirrhosis," *Digestive Diseases and Sciences* 52 (2007): 1187–1193.

22. M. A. Kern, D. Schubert, D. Sahi, et al., "Proapoptotic and Antiproliferative Potential of Selective Cyclooxygenase-2 Inhibitors in Human Liver Tumor Cells," *Hepatology* 36 (2002): 885–894.

23. P. Marquardt, Y. Hoshida, and A. G. Singal, "Aspirin: Does it Have a Role for Chemoprevention of Hepatocellular Carcinoma?," *Gastroenterology* 156 (2019): 1530–1531.

24. T. G. Simon, Y. Ma, J. F. Ludvigsson, et al., "Association Between Aspirin Use and Risk of Hepatocellular Carcinoma," *JAMA Oncology* 4 (2018): 1683–1690.

25. P. G. Venkatesh, S. Parasa, B. Njei, M. R. Sanaka, and U. Navaneethan, "Increased Mortality With Peptic Ulcer Bleeding in Patients With Both Compensated and Decompensated Cirrhosis," *Gastrointestinal Endoscopy* 79 (2014): 605–614.e3.

26. S. L. Zheng and A. J. Roddick, "Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-Analysis," *Journal of the American Medical Association* 321 (2019): 277–287.

27. A. Tripodi, "Hemostasis in Acute and Chronic Liver Disease," *Seminars in Liver Disease* 37 (2017): 28–32.

28. E. S. Huang, L. L. Strate, W. W. Ho, S. S. Lee, and A. T. Chan, "Long-Term Use of Aspirin and the Risk of Gastrointestinal Bleeding," *American Journal of Medicine* 124 (2011): 426–433.

29. T. Y. Lee, Y. C. Hsu, H. C. Tseng, J. T. Lin, M. S. Wu, and C. Y. Wu, "Association of Daily Aspirin Therapy With Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis C Virus Infection," *Clinical Gastroenterology and Hepatology* 18 (2020): 2784–2792.e7.

30. L. A. García Rodríguez, M. Martín-Pérez, C. H. Hennekens, P. M. Rothwell, and A. Lanas, "Bleeding Risk With Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies," *PLoS ONE* 11 (2016): e0160046.

31. S. P. Dehmer, M. V. Maciosek, T. J. Flottemesch, A. B. LaFrance, and E. P. Whitlock, "Aspirin for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: A Decision Analysis for the U.S. Preventive Services Task Force," *Annals of Internal Medicine* 164 (2016): 777–786.

32. L. E. Lévesque, J. A. Hanley, A. Kezouh, and S. Suissa, "Problem of Immortal Time Bias in Cohort Studies: Example Using Statins for Preventing Progression of Diabetes," *BMJ* 340 (2010): b5087.

33. KASL Clinical Practice Guidelines for Management of Chronic Hepatitis B," *Clinical and Molecular Hepatology* 28 (2022): 276–331.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information. **Figure S1:** Flow diagram of patient selection. **Figure S2:** Cumulative incidences of all-cause mortality (A) and liver-related mortality (B) according to the aspirin-use status. Gray's test was used to compare cumulative incidences between aspirin users and nonusers. **Table S1:** ICD-10 diagnostic codes for definition of disease. **Table S2:** Risk of all-cause and liver-related mortality according to the aspirin-use status (after PS matching). **Table S3:** Risk of HCC according to the aspirin-use status with different definition (before and after PS matching). **Table S4:** Risk of GI bleeding according to the aspirin-use status with different definition (before and after PS matching). **Table S5:** Risk of HCC and GI bleeding according to the aspirin continuation vs. discontinuation (1-year and 3-year cutoff).