International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Daily Antiplatelets Other Than Aspirin Reduce Liver Cancer Risk but Increase Intracranial Hemorrhage Risk in Cirrhotic Patients

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Purpose: Aspirin, known to reduce the risk of liver cancer, has been proposed as a preventive measure for patients with chronic hepatitis and cirrhosis. However, concerns regarding aspirin's potential to cause gastrointestinal (GI) mucosal injury and bleeding have emerged. Several antiplatelets other than aspirin (APOA) that pose a smaller risk of GI bleeding than aspirin have been proposed as potential aspirin substitutes. This study investigated whether APOAs were effective at reducing the risk of hepatocellular carcinoma (HCC). Additionally, we evaluated the safety of APOAs, specifically regarding their potential to increase the risk of GI bleeding, in a nationwide cirrhosis cohort.

Patients and Methods: For the period January 1, 2000, to December 31, 2017, we identified 686 993 patients with cirrhosis from a national database. A control group was established using 1:2 propensity score matching on the basis of sex, age, comorbidities, and medication use.

Results: Daily use of APOAs was significantly associated with lower incidences of HCC (aHR 0.67; 95% CI, 0.60–0.73; P < 0.001) and showed no significant increase in GI bleeding risk (aHR 1.04; 95% CI, 0.93–1.15; P = 0.533) compared to nonuse of APOAs. However, the risks of intracranial hemorrhage (aHR, 1.41; 95% CI, 1.18 to 1.69; $P < 0.001$) and overall mortality (aHR, 2.03; 95% CI, 1.95 to 2.10; $P < 0.001$) were higher in the APOA user group.

Conclusion: Our results suggest that although daily use of APOAs other than aspirin may decrease the HCC risk of patients with cirrhosis, it may also increase their risks of intracranial hemorrhage and overall mortality. Therefore, the use of APOAs as an alternative to aspirin for HCC prevention in patients with cirrhosis requires careful consideration.

Keywords: cirrhosis, antiplatelet agents, hepatocellular carcinoma, intracranial hemorrhage, mortality

Introduction

Platelets are multifunctional cell fragments participating in immune response, inflammation, allergic reaction, tissue regeneration, and lymphangiogenesis and are key in carcinogenesis and metastasis.[1–3] Tumor cell dissemination is enhanced by platelets, which recruit immune cells to tumor sites (both primary and metastatic) and activate endothelial cell function.[1] Platelet activation increases the risk of prothrombotic events and contributes to progression and metastasis of cancer.[2] Tumor cell proliferation is promoted by activated platelets. These platelets contribute to adverse tumor–stroma crosstalk, which fuels tumor progression.[4] Conversely, platelets can also be activated by cancer cells for the purpose of enhancing thrombus formation.[1] By modulating platelet function, cancer cells can directly induce platelet–tumor aggregation, trigger the release of platelet granules, and alter the turnover of platelets.

Received: 30 May 2024
Accepted: 5 October 2024
Published: 17 October 2024

Platelets promote the proliferation and invasion of hepatocellular carcinoma (HCC) cells. Their involvement encompasses not only direct effects on tumor cells but also a contribution to profibrinogenic signaling, an immune response in the liver, and interactions among these factors in the stroma.[5]

Treatment with antiplatelet agents can reduce cancer incidence.[6] Antiplatelet agents use was shown to be associated with reduced cancer risk in patients with diabetes.[7] Among the drugs investigated, nonsteroidal anti-inflammatory drugs (NSAIDs)—not including aspirin—were the ones found to lead to a significant decrease in inflammation risk (HR, 0.73). HCC recurrence risk is lower 21% after treatment with NSAIDs,[6,8] and NSAIDs can reduce 19% the risk of HCC.[9]

Antiplatelet agents reduce HCC risk for patients with effectively suppressed hepatitis B.[10,11] The antiplatelets other than aspirin (APOA) (clopidogrel) may cause gastrointestinal (GI) bleeding.[10,12] NSAIDs may cause colonic diverticular bleeding.[13]

Liver cancers, particularly HCC, are primarily caused by cirrhosis. Patients with cirrhosis are more likely than those without cirrhosis to experience GI bleeding. Daily aspirin use reduces HCC incidence; however, aspirin is known to precipitate GI bleeding, although likely not to a severe degree (ie, grade 3 or higher bleeding); the incidence of severe bleeding was not higher in patients treated with sorafenib using aspirin to prevent gastrointestinal cancer than in patients not taking aspirin.[14] Whether APOAs can safely replace aspirin for the prevention of HCC in cirrhotic patients must be investigated. Therefore, this study investigated, within a nationwide cohort, whether daily use of APOAs was as effective as daily use of aspirin for reducing HCC incidence without increasing the incidence of GI bleeding.

Materials and Methods

Institutional Review Board Statement

- Research Protocol and Institutional Review Board Approvals: All personal information was protected by delinking identifying information from the main data set. All information was made available only to the researchers. The data analyzed were anonymous, and the primary data were collected in accordance with epidemiological guidelines. The study was approved by the Research Ethics Committee of Chang Gung Medical University and Hospital in Taoyuan, Taiwan (202100464B0).

HCC Study

In total, 686 993 patients with cirrhosis from 2000 to 2017 were identified in the National Health Insurance Research Database in Taiwan (Figure 1).

In the APOA group, patients were excluded if (1) they had received a cancer diagnosis, including for cancer of the GI tract, before the index date (n = 19 664); (2) they were aged <18 years (n = 33 611); (3) their sex was unknown (n = 4198); or (4) they had a history of daily use of a statin, metformin, or aspirin after receiving a diagnosis of cirrhosis (n = 234 783). Patients who had not been using an APOA for at least 90 days after receiving a diagnosis of cirrhosis were also excluded. After these exclusions were applied, 5600 APOA users and 11 200 APOA nonusers were enrolled. Metformin and statin use have been shown to reduce HCC incidence by 50%-68% and 42% - 69%, respectively.[15–17]

Sonography, CT, and MRI were performed every 3 to 6 months. Serum alpha-fetoprotein (AFP) measurements were taken every 3 to 6 months.

HCC was the main outcome. Follow-up ended at HCC diagnosis, death, withdrawal from the Taiwan National Health Insurance program, or December 31, 2018. We employed GI bleeding as the secondary outcome.

Definitions and Codes

Comorbidities were defined and recorded on the basis of the 9th and 10th editions of the *International Classification of Diseases* (*ICD*; Table S1); drugs were identified on the basis of Anatomical Therapeutic Chemical (ATC) codes (Table S2). Cirrhosis and decompensated cirrhosis were also identified using *ICD* codes.

Comorbidities were defined as one hospital admission or at least five outpatient visits with the corresponding *ICD* code within the 1 year after the first diagnosis of cirrhosis. Cirrhosis was defined as one hospital admission or ≥3 outpatient visits with the corresponding *ICD* code.

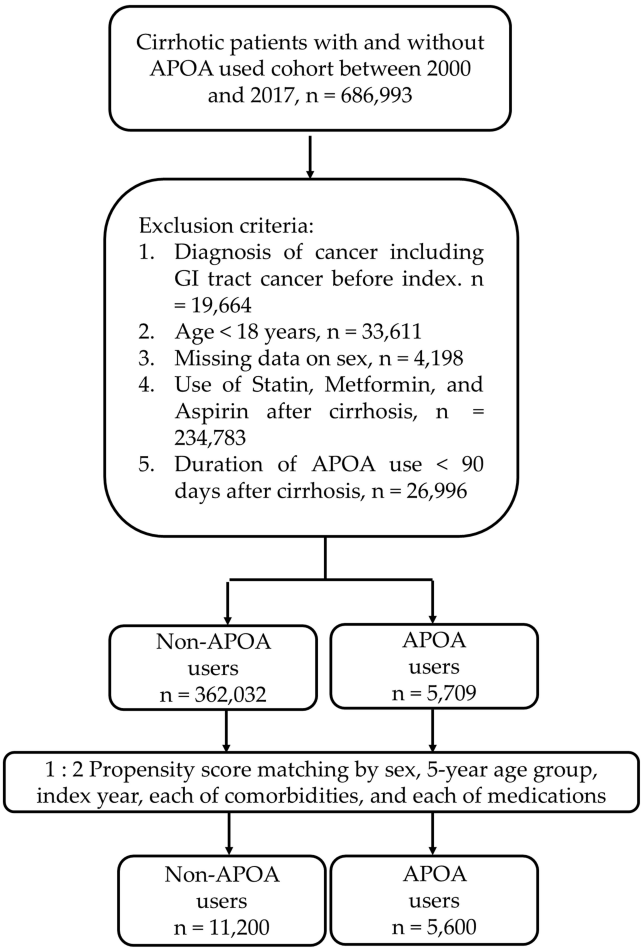

Figure 1 Patient enrollment process.

The use of aspirin (≥90 days for the aspirin cohort) and other drugs (≥1 day within the 90 days before cirrhosis) was identified on the basis of ATC codes B01AC06, B01AC30, B01AC56, N02BA01, and N02BA51. The use of APOAs (≥90 days for the APOA cohort) was identified on the basis of all ATC B01AC codes, excluding those indicating aspirin (Table S2). Cases with drug use less than 90 days before cirrhosis index date were excluded.

We performed adjustments on the basis of sex, age, medication use, and comorbidities.

Statistical Analysis

We compared the demographic variables, comorbidities, and medications of the APOA users and nonusers by using Student's *t* test (continuous variables) and the chi-square test (categorical variables). We compared risks between APOA users and nonusers by using Cox proportional hazard models. We conducted propensity score matching (PSM). Univariable Cox proportional hazard models were utilized to estimate hazard ratios (HRs) and their associated 95% CIs. Adjusted hazard ratios (aHRs) were calculated using multivariable Cox proportional hazard models, with adjustments on the basis of age, sex, comorbidities, and medication use. Cumulative incidences of HCC and GI bleeding in both cohorts were identified by Kaplan–Meier analysis, and the Log rank test was employed to test for inter cohort differences. Two-sided *P* values of <0.05 indicated statistical significance. SAS version 9.4 (SAS Institute, Cary, NC, USA) was employed for the data analyses.

Results

HCC Incidence in Patients with Cirrhosis with or Without APOA Use

We matched patients on the basis of possible confounding factors, namely sex, age, comorbidities (cardiovascular disease [CVD], cerebral vascular accident [CVA], hepatitis B virus [HBV], hepatitis C virus [HCV], and diabetes mellitus [DM]), and the use of medications (interferons, nucleoside analogs, and direct-acting antivirals [DAAs]) and compared the baseline characteristics of the APOA users and nonusers (Table 1).

Male sex ($P < 0.001$; aHR, 1.24; 95% CI, 1.15 to 1.33), DM ($P < 0.001$; aHR, 1.55; 95% CI, 1.44 to 1.66), compensated cirrhosis ($P < 0.001$; aHR, 1.49; 95% CI, 1.39 to 1.60), HBV ($P < 0.001$; aHR, 1.74; 95% CI, 1.6 to 1.88), and HCV ($P < 0.001$; aHR, 2.57; 95% CI, 2.38 to 2.77) were significant risk factors for HCC in both the APOA users and nonusers. CVA ($P < 0.001$; aHR, 0.89; 95% CI, 0.82 to 0.0.96), nucleoside analog use ($P < 0.001$; aHR, 0.36; 95% CI, 0.28 to 0.045), and DAA use ($P < 0.01$; aHR, 0.55; 95% CI, 0.36 to 0.86) were significantly associated with a lower risk of HCC incidence in both the APOA users and nonusers (Table 2). In a previous study, individuals with decompensated cirrhosis (n = 56), decompensated cirrhosis with

Table 1 Baseline Characteristics of APOA Users and Nonusers

	Liver Cirrhosis Without Apoa User (N=11200)		Liver Cirrhosis with Apoa User (N=5600)		
Variables	**n**	**%**	**n**	**%**	**P-value**
Sex					0.143
Female	4011	35.81	2070	36.96	
Male	7189	64.19	3530	63.04	
Age group (year)					0.657
< 35	180	1.61	94	1.68	
35–44	412	3.68	229	4.09	
45–54	1177	10.51	602	10.75	
55–64	176	1.57	73	1.30	
65–74	3914	34.95	1960	35.00	
75–84	3338	29.80	1639	29.27	
85+	2003	17.88	1003	17.91	
Liver cirrhosis					
Compensated	2951	26.35	1544	27.57	0.091
Decompensated	8249	73.65	4056	72.43	0.091
Comorbidities					
Cardiovascular disease	6154	54.95	3027	54.05	0.273
Cerebrovascular accident	5173	46.19	2516	44.93	0.123
Diabetes mellitus	4172	37.25	2030	36.25	0.205
Hepatitis B virus	2141	19.12	1065	19.02	0.879
Hepatitis C virus	2162	19.30	1084	19.36	0.934

(*Continued*)

Table 1 (Continued).

	Liver Cirrhosis Without Apoa User (N=11200)		Liver Cirrhosis with Apoa User (N=5600)		
Variables	**n**	**%**	**n**	**%**	**P-value**
Medication					
Nucleoside analogue	408	3.64	196	3.50	0.639
Interferon	110	0.98	49	0.88	0.499
DAA	140	1.25	70	1.25	1.000
	Mean	**SD**	**Mean**	**SD**	
Age, year	70.64	14.72	70.56	14.93	0.736
Follow-up, year	4.18	3.61	2.48	3.44	0.763

Note: Student's *t* test.
Abbreviations: APOA, antiplatelets other than aspirin; DAA, direct-acting antiviral; SD, standard deviation.

Table 2 Risk of HCC in Cirrhotic Patients with or Without APOA Use

	HCC								
Daily APOA	**Event**	**py**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
No	2648	46,863	56.51	1	(reference)		1	(reference)	
Yes	493	13,881	35.52	0.61	(0.55, 0.67)	<0.001	0.67	(0.6, 0.73)	<0.001
Sex									
Female	1093	21,573	50.67	1	(reference)		1	(reference)	
Male	2048	39,172	52.28	1.03	(0.96, 1.11)	0.371	1.24	(1.15, 1.33)	<0.001
Age group (year)									
< 35	10	2223	4.5	1	(reference)		1	(reference)	
35–44	50	3870	12.92	2.9	(1.47, 5.71)	0.002	2.81	(1.43, 5.55)	0.003
45–54	318	9196	34.58	7.78	(4.14, 14.61)	<0.001	6.8	(3.62, 12.77)	<0.001
55–64	56	1157	48.42	10.9	(5.58, 21.46)	<0.001	8.76	(4.46, 17.2)	<0.001
65–74	1539	21,984	70	15.6	(8.38, 29.1)	<0.001	12.03	(6.44, 22.45)	<0.001
75–84	948	15,228	62.26	13.7	(7.38, 25.71)	<0.001	11	(5.88, 20.59)	<0.001
85+	220	7086	31.05	6.73	(3.56, 12.7)	<0.001	6.48	(3.42, 12.26)	<0.001
Liver cirrhosis									
Compensated	1192	15,301	77.9	1.81	(1.68, 1.94)	<0.001	1.49	(1.39, 1.60)	<0.001
Decompensated	1949	45,443	42.89	0.55	(0.51, 0.59)	<0.001	0.67	(0.62, 0.72)	<0.001

(*Continued*)

Table 2 (Continued).

	HCC								
Daily APOA	**Event**	**py**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
Comorbidities									
Cardiovascular disease	1719	29,426	58.42	1.26	(1.18, 1.36)	<0.001	1.04	(0.97, 1.12)	0.276
Cerebrovascular accident	1241	23,081	53.77	1.04	(0.97, 1.12)	0.297	0.89	(0.82, 0.96)	0.002
Diabetes mellitus	1372	18,301	74.97	1.77	(1.65, 1.9)	<0.001	1.55	(1.44, 1.66)	<0.001
Hepatitis B virus	896	12,472	71.84	1.55	(1.44, 1.68)	<0.001	1.74	(1.6, 1.88)	<0.001
Hepatitis C virus	1156	10,177	113.59	2.87	(2.67, 3.08)	<0.001	2.57	(2.38, 2.77)	<0.001
Medication									
Nucleoside analogue	80	4038	19.81	0.38	(0.3, 0.47)	<0.001	0.36	(0.28, 0.45)	<0.001
Interferon	60	1029	58.3	1.17	(0.91, 1.51)	0.228	1.4	(0.88, 2.23)	0.156
DAA	67	1216	55.1	1.1	(0.86, 1.4)	0.451	0.55	(0.36, 0.86)	0.009

Notes: adjusted for sex, age, comorbidities, and medication use.
Abbreviations: aHR, adjusted hazard ratio; APOA, antiplatelets other than aspirin; cHR, crude hazard ratio; DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; IR, incidence rate per 1000 person-years; PY, person-years.

prominent ascites (n = 28), and decompensated cirrhosis with rupture of esophageal varices (n = 14) had 5-year survival rates of 32.9% ± 6.9%, 20.6% ± 8.4%, and 29.4 ± 13.4%, respectively.[18] In our study, the 5-year incidence of HCC was approximately 30% (Figure 2). The finding that patients with decompensated cirrhosis have lower life expectancy compared with those with compensated cirrhosis may explain why we did not discover a correlation between decompensated cirrhosis and HCC incidence. These patients may have reduced overall survival related to the decompensated cirrhosis before any HCC development event.

The cumulative HCC risk in APOA users and nonusers (excluding patients dead before cancer development) was also significance reduce HCC incidence (aHR, 0.70, 95% CI, 0.64 to 0.78), $P < 0.001$ (Table S3).

Long-Term Daily Use of APOA Reduced HCC Incidence

From the total treatment duration (in days) of APOA in the study period, this study calculated the cumulative days of APOA for each user. We then divided cumulative days into quartiles. We performed 1:2 PSM and then compared HCC incidence between

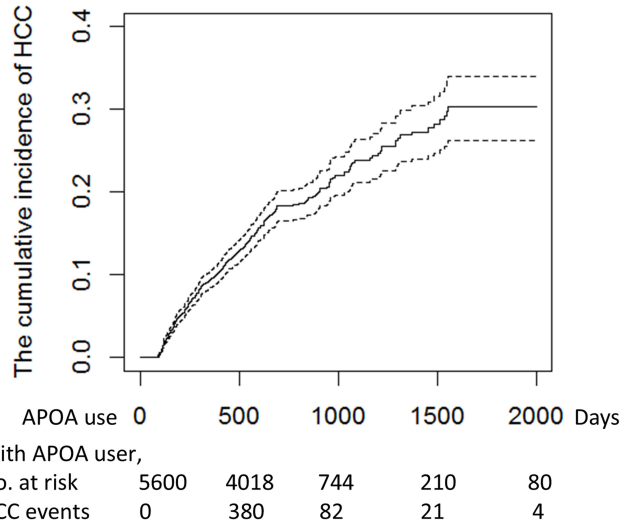

Figure 2 Cumulative HCC incidence in patients receiving antiplatelets other than aspirin (APOAs).

APOA users and nonusers. APOA users were found to be less likely to have developed HCC after 436 days ($P < 0.001$; aHR, 0.69; 95% CI, 0.58 to 0.82; Table 3).

This study discovered an association between APOA use and lower incidence of HCC in patients with compensated or decompensated cirrhosis (Tables 4 and 5).

Clopidogrel (Plavix) and Other APOAs Reduced HCC Incidence

Clopidogrel (Plavix) and other APOAs reduced HCC incidence ($P < 0.001$; aHR: 0.26; 95% CI, 0.17 to 0.40; Table S4).

Daily APOA Use Did Not Significantly Increase GI Bleeding Incidence

Patients using metformin, statins, or aspirin and those who had not been using an APOA for at least 90 days were excluded from this study's analysis. The incidence of GI bleeding was compared between the 5600 APOA users and 11 200 APOA nonusers who had undergone 1:2 PSM by index year, sex, 5-year age group, comorbidities (CVD, CVA, DM, HBV, and HCV), and use of medications (nucleoside analogs, interferon, DAAs). We did not find a significant association of APOA use with a greater incidence of GI bleeding ($P = 0.533$; HR, 1.04; 95% CI, 0.93 to 1.15; Table 6 and Table S5).

Table 3 Correlation of the Duration of APOA Use with the Risk of HCC in Cirrhotic Patients

	HCC								
Daily APOA	**n**	**PY**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
No	2648	46,863	56.51	1	(Reference)		1	(Reference)	
Yes (days)									
90–134	114	4075	27.98	0.49	(0.4, 0.59)	<0.001	0.55	(0.46, 0.67)	<0.001
135–215	112	3364	33.29	0.57	(0.47, 0.69)	<0.001	0.64	(0.53, 0.77)	<0.001
216–436	133	2965	44.86	0.76	(0.64, 0.9)	0.002	0.8	(0.67, 0.96)	0.0135
>436	134	3477	38.54	0.66	(0.56, 0.79)	<0.001	0.69	(0.58, 0.82)	<0.001

Notes: adjusted for sex, age, comorbidities, and medication use.
Abbreviations: aHR, adjusted hazard ratio; APOA, antiplatelets other than aspirin; cHR, crude hazard ratio; HCC, hepatocellular carcinoma; IR, incidence rate per 1000 person-years; PY, person-years.

Table 4 Risk of HCC Among Patients with Compensated Cirrhosis, with or Without APOA Use

	HCC								
Daily APOA	**n**	**PY**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
no	1013	12,023	84.25	1	(Reference)		1	(Reference)	
Yes (days)									
90–134	40	834	47.98	0.55	(0.4, 0.75)	<0.001	0.59	(0.43, 0.81)	0.001
135–215	45	726	61.96	0.7	(0.52, 0.94)	0.017	0.7	(0.52, 0.94)	0.019
216–436	48	813	59.06	0.67	(0.5, 0.9)	0.007	0.71	(0.53, 0.95)	0.021
>436	46	905	50.83	0.58	(0.43, 0.78)	<0.001	0.62	(0.46, 0.83)	0.001

Notes: adjusted for sex, age, comorbidities, and medication use.
Abbreviations: aHR, adjusted hazard ratio; APOA, antiplatelets other than aspirin; cHR, crude hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; IR, incidence rate per 1000 person-years; PY, person-years.

Table 5 Risk of HCC in Patients with Decompensated Cirrhosis, with or Without APOA Use

	HCC								
Daily APOA	**n**	**PY**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
No	1635	34,840	46.93	1	(Reference)		1	(Reference)	
Yes (days)									
90–134	74	3241	22.83	0.48	(0.38, 0.61)	<0.001	0.55	(0.44, 0.7)	<0.001
135–215	67	2638	25.4	0.53	(0.41, 0.67)	<0.001	0.61	(0.48, 0.78)	<0.001
216–436	85	2152	39.5	0.8	(0.65, 1)	0.051	0.86	(0.69, 1.07)	0.18
>436	88	2572	34.22	0.71	(0.57, 0.88)	0.002	0.73	(0.59, 0.9)	0.004

Notes: adjusted for sex, age, comorbidities, and medication use.
Abbreviations: aHR, adjusted hazard ratio; APOA antiplatelets other than aspirin; cHR, crude hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; IR, incidence rate per 1000 person-years; PY, person-years.

Table 6 Risk of GI Bleeding in Cirrhotic Patients with or Without APOA Use, Demographics, Different Types of Liver Cirrhosis, Each of Comorbidities, and Each of Concomitant Medications

	GI bleeding								
Variables	**Event**	**py**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
Non- APOA	1956	35,333	5.54	1	(reference)		1	(reference)	
APOA	413	7843	5.27	0.94	(0.85, 1.05)	0.286	1.04	(0.93, 1.15)	0.533
Sex									
Female	859	15,256	5.63	1	(reference)		1	(reference)	
Male	1510	27,920	5.41	0.97	(0.89, 1.05)	0.433	1.08	(0.99, 1.17)	0.085
Age group (year)									
< 35	33	1862	1.77	1	(reference)		1	(reference)	
35–44	65	2804	2.32	1.26	(0.83, 1.92)	0.276	1.32	(0.87, 2.01)	0.198
45–54	237	6852	3.46	1.85	(1.29, 2.67)	<0.001	1.8	(1.25, 2.60)	0.0016
55–64	39	896	4.35	2.3	(1.45, 3.66)	<0.001	2.1	(1.31, 3.34)	0.0019
65–74	898	16,345	5.49	2.85	(2.02, 4.04)	<0.001	2.48	(1.74, 3.52)	<0.001
75–84	764	10,027	7.62	3.87	(2.73, 5.49)	<0.001	3.21	(2.25, 4.58)	<0.001
85+	333	4390	7.59	3.78	(2.63, 5.41)	<0.001	3.15	(2.18, 4.54)	<0.001
Liver cirrhosis									
Compensated	641	11,442	5.6	1.03	(0.94, 1.13)	0.494	0.95	(0.87, 1.04)	0.268
Decompensated	1728	31,734	5.45	0.97	(0.89, 1.06)	0.494	1.05	(0.96, 1.16)	0.268
Comorbidities									
Cardiovascular disease	1288	19,501	6.6	1.4	(1.29, 1.52)	<0.001	1.08	(0.99, 1.18)	0.084
Cerebrovascular accident	1045	14,693	7.11	1.46	(1.35, 1.59)	<0.001	1.16	(1.07, 1.27)	<0.001
Diabetes mellitus	864	12,404	6.97	1.37	(1.26, 1.50)	<0.001	1.19	(1.09, 1.30)	<0.001

(*Continued*)

Table 6 (Continued).

	GI bleeding								
Variables	**Event**	**py**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
Hepatitis B virus	365	9212	3.96	0.68	(0.61, 0.76)	<0.001	0.87	(0.77, 0.98)	0.018
Hepatitis C virus	427	7202	5.93	1.08	(0.97, 1.20)	0.145	1.05	(0.95, 1.18)	0.345
Medication									
Nucleoside analogue	54	2858	1.89	0.35	(0.27, 0.46)	<0.001	0.53	(0.40, 0.71)	<0.001
Interferon	29	814	3.56	0.67	(0.46, 0.96)	0.0295	0.75	(0.38, 1.46)	0.391
DAA	38	900	4.22	0.79	(0.57,1.08)	0.138	1.24	(0.69, 2.24)	0.469

Notes: Multivariate models including APOAs, sex, age group, liver cirrhosis, each of comorbidities, and each of concomitant medications.
Abbreviations: aHR, adjusted hazard ratio; APOA, antiplatelets other than aspirin; cHR, crude hazard ratio; CI, confidence interval; DAA, direct-acting antivirals; GI, gastrointestinal tract; IR, incidence rate per 100 person-years; PY, person-years.

Daily APOA Use Increased Intracranial Hemorrhage Incidence

The incidence of intracranial hemorrhage was higher among the APOA users than among the APOA nonusers ($P < 0.001$, aHR, 1.41, 95% CI, 1.18 to 1.69, Table 7).

Daily APOA Use Reduced Overall Survival

The APOA users had a 2-fold higher mortality risk than did the APOA nonusers ($P < 0.001$, aHR, 2.03, 95% CI, 1.95 to 2.10, Table 8).

Discussion

Male sex and history of CVA, DM, compensated cirrhosis, HBV, or HCV are risk factors for HCC. Antiviral therapies (nucleoside analogs for HBV and DAA for HCV) were protective factors for HCC, regardless of the use of antiplatelet agents. The increased HCC risk in patients with cirrhosis and HBV, HCV, or DM may be attributable to chronic

Table 7 Risk of Intracranial Hemorrhage in Cirrhotic Patients with or Without APOA Use

	Intracranial hemorrhage								
Daily APOA	**Event**	**py**	**IR**	**cHR**	**(95% CI)**	***p*-value**	**aHR**	**(95% CI)**	***p*-value**
no	435	46,932	0.93	1	(reference)		1	(reference)	
yes	170	13,787	1.23	1.27	(1.07, 1.52)	0.008	1.41	(1.18, 1.69)	<0.001

Notes: adjusted for sex, age, comorbidities, and medication use.
Abbreviations: aHR, adjusted hazard ratio; APOA, antiplatelets other than aspirin; cHR, crude hazard ratio; CI, confidence interval; IR, incidence rate per 100 person-years; PY, person-years.

Table 8 Risk of Overall Mortality in Cirrhotic Patients with or Without APOA Use

	Overall Mortality								
Daily APOA	**Event**	**py**	**IR**	**cHR**	**(95% CI)**	**p-value**	**aHR**	**(95% CI)**	**p-value**
no	7733	51,102	15.1	1	(reference)		1	(reference)	
yes	4185	14,926	28	1.75	(1.69, 1.82)	<0.001	2.03	(1.95, 2.10)	<0.001

Notes: adjusted for sex, age, comorbidities, and medication use.
Abbreviations: aHR, adjusted hazard ratio; APOA, antiplatelets other than aspirin; cHR, crude hazard ratio; CI, confidence interval; IR, incidence rate per 100 person-years; PY, person-years.

inflammation, which has been shown to promote cancer development.[19,20] Conversely, the anti-inflammatory agents (nucleoside analogs) was associated with lower HCC incidence.[21,22] Our patients with cirrhosis and CVA (ischemia stroke) had a lower incidence of HCC than cirrhotic patients without CVA, possibly due to the use of an antiplatelet agents (eg, aspirin or clopidogrel) to prevent stroke recurrence.[23] Treatment with antiplatelet agents (including aspirin) was associated with a reduced risk of many kinds of cancers.[7]

NSAIDs and APOAs, including aspirin, may reduce HCC risk and prevent HCC recurrence.[6,24] One study revealed that NSAIDs significantly reduce the HCC recurrence risk (HR, 0.79).[9]

In a murine model, platelet antagonists and thrombocytopenia reduced the likelihood of tumor metastasis. This indirectly supports the positive role of inhibition of COX-1 in platelets in cancer treatment and prevention.[7]

Clopidogrel, by attenuating platelet activation and platelet–tumor cell binding, triggers hepatoma cell differentiation. Knockdown of transcription factor 4 promotes differentiation of HepG2 cells and inhibition of tumor formation. Transcription factor 4 is a potential downstream target of clopidogrel treatment.[25]

In the chronic phase of HBV infection, treatment with clopidogrel and aspirin reduces the number of intrahepatic CD8 (+) T cells that are specific to HBV and the number of inflammatory cells that are not specific to HBV. This treatment also decreases the HCC risk and severity of liver fibrosis.[26] In a study involving mice with chronic HBV, antiplatelet agents (clopidogrel and aspirin) decreased hepatic fibrosis severity and reduced the risk of hepatic fibrosis by 32% (adjusted pooled odds ratios (OR), 0.68; $P < 0.001$).[27]

Thrombotic and inflammatory complications have been associated with CVD, DM, cancer, and other chronic disorders.[28] APOAs work by blocking the P2Y12 receptor, thereby inhibiting platelet activation and adhesion; this helps to prevent thrombotic occlusion of atherosclerotic arteries caused by adenosine diphosphate.[29] The P2Y12 receptor is a type of adenosine diphosphate receptor found on the surface of platelets. It plays a role in regulating thrombus stability. Inhibitors of P2Y12—such as ticlopidine, clopidogrel, prasugrel, ticagrelor, and cangrelor—can either indirectly block this receptor or directly inhibit its function. Thienopyridine-derived nitrosothiols are bioactive compounds that irreversibly inhibit the binding of adenosine diphosphate to the receptor. This leads to decreased platelet aggregation and activation and reduces the activation of platelet aIIbβ3 integrins.[1] Furthermore, anti-inflammatory agents may inhibit tumor growth at the primary site, and antithrombotic agents may help prevent metastasis.[30]

Notably, NSAIDs and antiplatelet agents, including aspirin and clopidogrel, increase the risk of GI bleeding, including colonic diverticular bleeding.[12,13,31] The ORs for GI bleeding were 1.96 for NSAID use, 1.40 for peptic ulcer disease, and 3.20 for dual antiplatelet therapy. Because scholars have found associations of antiplatelet agents and NSAIDs with increased GI bleeding risk, identifying predictors of such bleeding may help in the optimization of treatment strategies.[32] In a study on the use of clopidogrel for stroke prevention and involving a dual antiplatelet therapy (cilostazol + clopidogrel) group and a clopidogrel monotherapy group was observed at a rate of 2.31 and a rate of 5.19 per 100 patient-years in the two groups, respectively. The combination of cilostazol and clopidogrel more significantly reduced 55% the ischemic stroke recurrence than clopidogrel monotherapy, the severe or life-threatening hemorrhage did no significantly different between the 2 groups, HR, 0.730 [95% CI, 0.206–2.588].[33] In our study, APOA use was not significantly associated with an increase in GI bleeding risk (P = 0.533; aHR, 1.04; 95% CI, 0.93 to 1.15). However, clinicians should be careful about potential increases in intracranial hemorrhage risk and overall mortality risk resulting from the use of antiplatelets other than aspirin. The risks of early mortality and poor functional outcomes are increased in patients with an antiplatelet therapy–related intracranial hemorrhage.[34,35] Importantly, intracranial hemorrhage survivors were more likely to have an ischemic event than intracranial hemorrhage recurrence, 6.8 per 100 person-years and an annual incidence of 3.0% versus 2.6 per 100 person-years and an annual incidence of 2.4%, respectively.[34,36] Among patients with hyperlipidemia or those with stroke, antiplatelet therapy to prevent major thromboembolic complications can be safely restarted.[34] Older patients, patients with history of cerebrovascular accidents, and patients with diabetes mellitus were associated with increased GI bleeding risk (Table 6). These risk factors might also suggest a potential tendency for intracranial hemorrhage, but further studies are needed to confirmed these observations. Further research is warranted to identify a specific subgroup of patients with cirrhosis at high risk of intracranial hemorrhage. Careful selection is necessary when considering the use of APOA in cirrhotic patients with a high risk of ICH, and this should be reflected in clinical practice. This subgroup should not receive daily anticoagulant therapy with an APOA

for the prevention of HCC. Our results raise concerns about the use of APOAs as an alternative to aspirin for HCC prevention in patients with cirrhosis.

The limitations of this study include the following. 1) APOAs have diverse mechanisms and different GI bleeding risk profiles. 2) This study divided patients into compensated and decompensated cirrhosis subgroups. Whether APOAs increase the risk of variceal bleeding in patients with cirrhosis could not be determined. 3) Several factors that are likely to raise a person's HCC risk, including nonalcoholic steatohepatitis status and alcohol consumption, were not included in the analysis because data on these factors were unavailable in the study period. 4) Our findings support the need for additional well-designed prospective studies to confirm the safety and benefits of using specific APOAs. These studies should focus on the prevention of HCC in patients with cirrhosis.

Conclusion

This study discovered that daily use of antiplatelets other than aspirin (APOA) can reduce the risk of HCC by 33% without increasing the GI bleeding risk but may increase the risks of intracranial hemorrhage and mortality. Additional well-designed prospective studies should be conducted to confirm that APOAs are suitable and effective for prevention of liver cancer in cirrhotic patients. Future studies should exclude patients at high risk of intracranial hemorrhage.

Data Sharing Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Informed Consent Statement

As this was a retrospective study based on the assessment of existing data, the committee waived the requirement for informed consent from the patients. All personal data were only available to investigators and were secured by delinking the recognition information from the main dataset.

Acknowledgments

This study is based in part on data from the National Health Insurance Research Database of the Ministry of Health and Welfare (H108195). The interpretations and conclusions contained herein do not represent the positions of the National Health Insurance Administration, Taiwan.

Funding

This research was funded by Chang Gung Memorial Hospital, grant number CFRPG3L0081.

Disclosure

The authors declare no conflicts of interest in this work.

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