original reports

H1-Antihistamines Reduce the Risk of Hepatocellular Carcinoma in Patients With Hepatitis B Virus, Hepatitis C Virus, or Dual Hepatitis B Virus-Hepatitis C Virus Infection

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abstract

PURPOSE H1-antihistamines (AHs) may exert protective effects against cancer. This study investigated the association of AH use with the risk of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV), hepatitis C virus (HCV), or dual HBV-HCV virus infection.

MATERIALS AND METHODS Patients with HBV, HCV, or dual HBV-HCV infection were enrolled from Taiwan's National Health Insurance Research Database and examined for the period from January 1, 2006, to December 31, 2015. We used the Kaplan-Meier method and Cox proportional hazards regression to evaluate the association between AH use and HCC risk.

RESULTS We included patients with HBV infection (n = 521,071), HCV (n = 169,159), and dual HBV-HCV (n = 39,016). Patients with HBV, HCV, or dual virus infection who used AHs exhibited significantly lower risk of HCC relative to patients who did not use AH, with their adjusted hazard ratio being 0.489 (95% CI, 0.455 to 0.524), 0.484 (95% CI, 0.450 to 0.522), and 0.469 (95% CI, 0.416 to 0.529), respectively. Furthermore, there was a dose-response relationship between AH use and the risk of HCC in the HBV cohort. The adjusted hazard ratios were 0.597 (95% CI, 0.530 to 0.674), 0.528 (0.465 to 0.600), 0.470 (0.416 to 0.531), and 0.407 (0.362 to 0.457) for AH use of 28-42, 43-63, 64-119, and ≥ 120 cumulative defined daily doses, respectively, relative to no AH use. Additionally, there was also a dose-response relationship between AH use and the risk of HCC in the HCV and dual HBV-HCV cohorts.

CONCLUSION AH use may reduce the risk for HCC among patients with HBV, HCV, or dual infection in a dose-dependent manner. Further mechanistic research is needed.

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INTRODUCTION

Histamines are biologically active substances that potentiate the inflammatory and immune responses[1] of the body and act as neurotransmitters.[2] Antihistamines (AHs) are drugs that antagonize these effects by blocking or inhibiting receptors (H-receptors).[3] They are categorized as either H1 or H2 AHs depending on the type of H-receptor that they target. H1-AHs are mostly used to treat allergic reactions and mast cell–mediated disorders, and they are among the most commonly used drugs worldwide for the treatment of allergic symptoms (eg, relief from hay fever). Recently, studies have used preclinical evidence to investigate the role of AHs as anticancer agents.[4-18] Multiple mechanisms have been proposed for this potential effect,[9,13-15,17] and they involve the use of antiproliferative, proapoptotic, and radiosensitizing properties; lysosomal cell death[9,19,20]; and immunologic pathways.[21,22] The effectiveness of anticancer therapy can be severely limited by specific tumor types or subtypes, and new and improved anticancer drugs are always required[23]; the repurposing of existing medication is a time- and cost-effective means of addressing this challenge.[24,25] AHs are safe drugs with minimal side effects that are well tolerated by most people; therefore, they are excellent candidates for repurposing as drugs for cancer therapy.

Hepatocellular carcinoma (HCC) is among the most common malignant tumors of the liver. It has higher incidences in East Asian countries such as Taiwan, China, and Japan, and lower incidences in Western countries. HCC is the second leading cause of cancer-related deaths in Taiwan and the fourth leading cause of cancer-related deaths worldwide.[26,27] The main

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

H1-antihistamines (AHs) may exert protective effects against cancer. This study investigated the association of AH use with the risk of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV), hepatitis C virus (HCV), or dual HBV-HCV virus infection.

Knowledge Generated

The results indicated that patients with HBV, HCV, or dual virus infections who used AH had an approximately two-fold lower risk of HCC when compared with patients who did not use AH. Our study is the first to report a dose-response relationship between AH use and HCC risk in patients with HBV, HCV, or dual virus infections after controlling for confounders.

Relevance

AH use may reduce HCC risk in patients with HBV, HCV, or dual infections in a dose-dependent manner. AH use is a potential adjuvant strategy for preventing HCC in patients with HBV, HCV, or dual infections.

causes of HCC are related to hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, nonalcoholic fatty liver disease, and cirrhosis.[28,29] Carriers of HBV infection are at substantial risk of HCC- and liver-related death compared with individuals without HBV.[30-33] The estimated risk of HCC is 15- to 20-fold higher in individuals with HCV relative to individuals without HCV. HCV carriers in the United States are at substantial risk of HCC and cancer-related death.[34] In a case report, Feng et al[35] found unexpected remission of HCC with lung metastasis to the

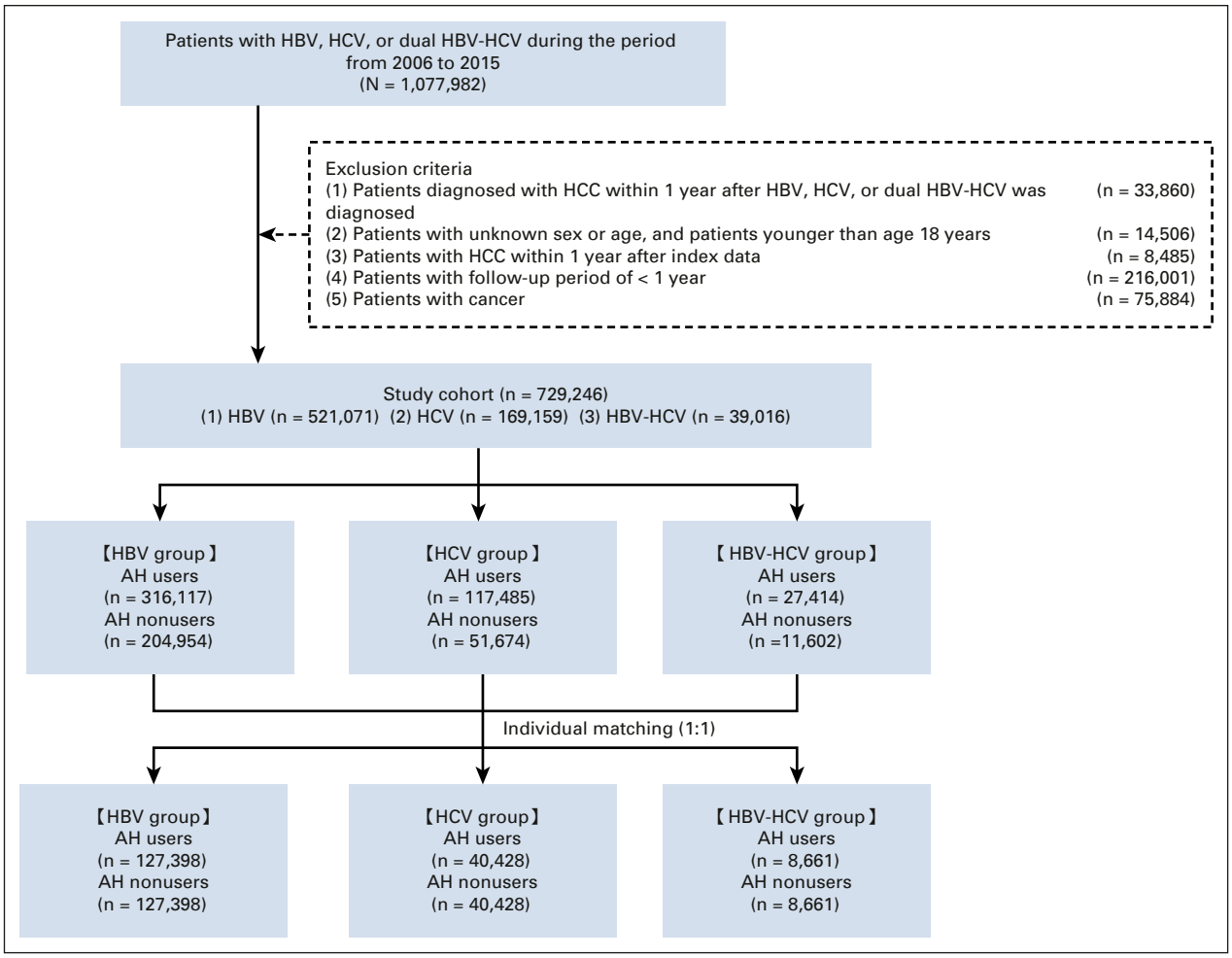

FIG 1. Flow chart of recruitment and data analysis. AH, antihistamine; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

TABLE 1. Characteristic Baseline of HBV, HCV, and Dual HBV-HCV Cohorts

Characteristic	HBV Cohort			HCV Cohort			Dual HBV-HCV Cohort		
	AH User n = 127,398 No. (%)	AH Nonuser n = 127,398 No. (%)	*P*	AH User n = 40,428 No. (%)	AH Nonuser n = 40,428 No. (%)	*P*	AH User n = 8,661 No. (%)	AH Nonuser n = 8,661 No. (%)	*P*
Sex			1.0000			1.0000			1.0000
Female	48,682 (38.21)	48,682 (38.21)		18,274 (45.2)	18,274 (45.2)		3,041 (35.11)	3,041 (35.11)	
Male	78,716 (61.79)	78,716 (61.79)		22,154 (54.8)	22,154 (54.8)		5,620 (64.89)	5,620 (64.89)	
Age group, years			.7864			.9778			.9973
18-30	12,514 (9.82)	12,503 (9.81)		1,549 (3.83)	1,506 (3.73)		357 (4.12)	360 (4.16)	
31-40	31,561 (24.77)	31,414 (24.66)		4,792 (11.85)	4,805 (11.89)		1,353 (15.62)	1,357 (15.67)	
41-50	34,477 (27.06)	34,821 (27.33)		7,368 (18.22)	7,388 (18.27)		1,861 (21.49)	1,851 (21.37)	
51-60	28,720 (22.54)	28,719 (22.54)		9,945 (24.60)	9,966 (24.65)		2,222 (25.66)	2,253 (26.01)	
61-70	13,163 (10.33)	12,999 (10.20)		8,278 (20.48)	8,228 (20.35)		1,646 (19.00)	1,616 (18.66)	
71-80	5,365 (4.21)	5,361 (4.21)		6,171 (15.26)	6,169 (15.26)		989 (11.42)	992 (11.45)	
> 80	1,598 (1.25)	1,581 (1.24)		2,325 (5.75)	2,366 (5.85)		233 (2.69)	232 (2.68)	
Median (IQR)	46 (19)	46 (19)	.9280	57 (22)	57 (22)	.9560	54 (21)	54 (21)	.9332
AH use			< .0001			< .0001			< .0001
Nonusers									
< 28 cDDDs	0 (0.00)	127,398 (100)		0 (0.00)	40,428 (100)		0 (0.00)	8,661 (100)	
Users									
28-42 cDDDs[a]	33,491 (26.29)	0 (0.00)		11,175 (27.64)	0 (0.00)		2,429 (28.05)	0 (0.00)	
43-63 cDDDs[a]	28,733 (22.55)	0 (0.00)		9,677 (23.94)	0 (0.00)		2,097 (24.21)	0 (0.00)	
64-119 cDDDs[a]	32,490 (25.50)	0 (0.00)		9,382 (23.21)	0 (0.00)		2,043 (23.59)	0 (0.00)	
≥ 120 cDDDs[a]	32,684 (25.66)	0 (0.00)		10,194 (25.22)	0 (0.00)		2,092 (24.15)	0 (0.00)	
Mean (SD)	123.51 (198.52)	0 (0)	< .0001	158.54 (247.87)	0 (0)	< .0001	155.16 (229.73)	0 (0)	< .0001
Median (IQR)	64.65 (80.37)	0 (0)	< .0001	81 (123.27)	0 (0)	< .0001	79.80 (118.10)	0 (0)	< .0001
Follow-up time									
Median (IQR)	4.53 (3.11)	4.28 (3.11)	< .0001	3.85 (3.22)	3.31 (2.90)	< .0001	4.42 (3.34)	3.72 (3.05)	< .0001
Comorbidity									
Cirrhosis	3,111 (2.44)	4,485 (3.52)	< .0001	2,150 (5.32)	3,058 (7.56)	< .0001	616 (7.11)	974 (11.25)	< .0001
Nonalcoholic liver disease	2,517 (1.98)	2,061 (1.62)	< .0001	747 (1.85)	552 (1.37)	< .0001	180 (2.08)	146 (1.69)	.0573
Alcoholic liver disease	962 (0.76)	816 (0.64)	.0005	499 (1.23)	509 (1.26)	.7513	129 (1.49)	141 (1.63)	.4617
Hypertension	27,465 (21.56)	21,293 (16.71)	< .0001	14,916 (36.90)	12,692 (31.39)	< .0001	2,697 (31.14)	2,289 (26.43)	< .0001
Chronic kidney disease	2,254 (1.77)	1,547 (1.21)	< .0001	2,134 (5.28)	1,818 (4.50)	< .0001	360 (4.16)	349 (4.03)	.6731

(continued on following page)

TABLE 1. Characteristic Baseline of HBV, HCV, and Dual HBV-HCV Cohorts (continued)

Characteristic	HBV Cohort			HCV Cohort			Dual HBV-HCV Cohort		
	AH User n = 127,398 No. (%)	AH Nonuser n = 127,398 No. (%)	*P*	AH User n = 40,428 No. (%)	AH Nonuser n = 40,428 No. (%)	*P*	AH User n = 8,661 No. (%)	AH Nonuser n = 8,661 No. (%)	*P*
Hyperlipidemia	19,520 (15.32)	15,559 (12.21)	< .0001	6,048 (14.96)	4,924 (12.18)	< .0001	1,168 (13.49)	941 (10.86)	< .0001
Diabetes mellitus	14,587 (11.45)	12,742 (10)	< .0001	8,393 (20.76)	7,719 (19.09)	< .0001	1,608 (18.57)	1,438 (16.60)	.0007
Medication									
Interferon	36 (0.03)	51 (0.04)	.1077	105 (0.26)	80 (0.20)	.0657	10 (0.12)	19 (0.22)	.0944
Nonaspirin NSAIDs	59,477 (46.69)	43,061 (33.80)	< .0001	23,056 (57.03)	18,074 (44.71)	< .0001	5,075 (58.60)	3,870 (44.68)	< .0001
Aspirin	18,789 (14.75)	14,478 (11.36)	< .0001	10,268 (25.40)	8,351 (20.66)	< .0001	2,091 (24.14)	1,571 (18.14)	< .0001
Statin	26,262 (20.61)	19,699 (15.46)	< .0001	8,569 (21.20)	6,638 (16.42)	< .0001	1,768 (20.41)	1,372 (15.84)	< .0001
Antiviral agent									
Adefovir	676 (0.53)	1,026 (0.81)	< .0001	3 (0.01)	5 (0.01)	.7265	29 (0.33)	50 (0.58)	.0179
Lamivudine	1,916 (1.50)	3,057 (2.40)	< .0001	193 (0.48)	125 (0.31)	.0001	167 (1.93)	227 (2.62)	.0022
Telbivudine	1,040 (0.82)	1,031 (0.81)	.8426	3 (0.01)	3 (0.01)	1.0000	70 (0.81)	69 (0.80)	.9321
Entecavir	8,508 (6.68)	8,845 (6.94)	.008	26 (0.06)	27 (0.07)	.8907	454 (5.24)	503 (5.81)	.1032
Tenofovir	2,758 (2.16)	2,431 (1.91)	< .0001	230 (0.79)	190 (0.47)	< .0001	285 (3.29)	237 (2.74)	.0329
Peginterferon	90 (0.07)	39 (0.03)	< .0001	4,809 (11.90)	3,186 (7.88)	<.0001	728 (8.41)	508 (5.87)	<.0001
Ribavirin	200 (0.16)	86 (0.07)	< .0001	11,349 (28.07)	7,227 (17.88)	<.0001	1,793 (20.70)	1,129 (13.04)	<.0001

Abbreviations: AH, antihistamine; cDDD, cumulative defined daily dose; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NSAID, nonsteroidal anti-inflammation drug; SD, standard deviation.

[a]Intervals of cDDDs in HBV cohort (28-42, 43-63, 64-119, and ≥ 120), HCV cohort (28-49, 50-84, 85-168, and ≥ 169), and HBV-HCV cohort (28-49, 50-84, 85-168, and ≥ 169).

combination therapy of thalidomide and cyproheptadine. A small retrospective study of 52 patients with advanced HCC (Child-Pugh Class A), the sorafenib-cyproheptadine group had higher median survival rate than the sorafenib alone group.[36] In a large retrospective study of 70,885 patients with HCC, Hsieh et al[37] revealed that cyproheptadine use improves survival rate in patients with HCC receiving palliative treatments or without treatment regardless of clinical stages, except clinical stage I-II HCC with curative modalities. In a cell model experiment, cyproheptadine was demonstrated to block cell cycle progression through the activation of p38 mitogen-activated protein kinases in HCC cells; this resulted in the inhibition of cell proliferation and apoptosis.[38] Our previous study demonstrated that deptropine (an AH) blocks the fusion of autophagosome and lysosome and, consequently, induced hepatoma cell death.[39] Zhao et al[40] revealed upregulation of histamine receptors promote tumor progression in HCC and He et al[41] found the possible antiviral effects of AHs in HCV. Despite the extensive application of targeted therapy, current treatments for advanced HCC remain unsatisfactory.[42] Therefore, researchers have been actively researching the development of effective targeted agents for HCC.

Considering the high incidence of HCC, widespread use of AHs, and lack of any large population-based study regarding the connection between AH use and HCC risk, we extracted data from Taiwan's National Health Insurance (NHI) Research Database to investigate whether AH use is associated with reduced HCC incidence among patients with HBV, HCV, or dual HBV-HCV infection.

MATERIALS AND METHODS

Data Source

Taiwan NHI system now provides insurance coverage to more than 23 million people in Taiwan (99.6% of Taiwan's

TABLE 2. IRRs and aHRs of Hepatocellular Carcinoma in HBV, HCV, and Dual HBV-HCV Cohorts

Variable	Events	Person-Years	IR	IRR	95% CI for IRR	aHR[a]	95% CI for HR
HBV cohort							
AH use							
Nonuser (< 28 cDDDs)	2,443	573,433	426.03	Ref.		Ref.	
User (≥ 28 cDDDs)	1,191	600,450.2	198.35	0.466***	0.434 to 0.499	0.489***	0.455 to 0.524
28-42 cDDDs	302	141,879.1	212.86	0.500***	0.443 to 0.563	0.597***	0.530 to 0.674
43-63 cDDDs	262	132,352.1	197.96	0.465***	0.409 to 0.528	0.528***	0.465 to 0.600
64-119 cDDDs	293	158,757.6	184.56	0.433***	0.384 to 0.489	0.470***	0.416 to 0.531
≥ 120 cDDDs	334	167,461.5	199.45	0.468***	0.418 to 0.525	0.407***	0.362 to 0.457
HCV cohort							
AH use							
Nonuser (< 28 cDDDs)	2,031	152,157.23	1,334.80	Ref.		Ref.	
User (≥ 28 cDDDs)	1,122	172,281.7	651.26	0.488***	0.454 to 0.525	0.484***	0.450 to 0.522
28-49 cDDDs[b]	280	42,344.04	661.25	0.495***	0.437 to 0.561	0.537***	0.474 to 0.608
50-84 cDDDs[b]	262	40,102.22	653.33	0.489***	0.430 to 0.557	0.518***	0.455 to 0.589
85-168 cDDDs[b]	264	41,475.33	636.52	0.477***	0.419 to 0.542	0.479***	0.420 to 0.545
≥ 169 cDDDs[b]	316	48,360.11	653.43	0.490***	0.435 to 0.551	0.425***	0.378 to 0.479
Dual HBV-HCV cohort							
AH use							
Nonuser (< 28 cDDDs)	767	35,414	2,165.81	Ref.		Ref.	
User (≥ 28 cDDDs)	432	40,781.18	1,059.31	0.489***	0.435 to 0.550	0.469***	0.416 to 0.529
28-49 cDDDs[b]	119	10,036.98	1,185.62	0.547***	0.451 to 0.664	0.588***	0.485 to 0.713
50-84 cDDDs[b]	98	9,605.03	1,020.30	0.471***	0.382 to 0.581	0.514***	0.418 to 0.632
85-168 cDDDs[b]	103	10,147.72	1,015.01	0.469***	0.382 to 0.576	0.415***	0.339 to 0.509
≥ 169 cDDDs[b]	112	10,991.45	1,018.97	0.470***	0.386 to 0.574	0.394***	0.322 to 0.481

NOTE. *$P < .05$, **$P < .01$, ***$P < .001$.

Abbreviations: AH, antihistamine; aHR, adjusted hazard ratio; cDDD, cumulative defined daily dose; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio; Ref., reference.

[a]Multivariate model adjusted for sex, age, comorbidity (cirrhosis, nonalcoholic liver disease, alcoholic liver disease, hypertension, chronic kidney disease, hyperlipidemia, and diabetes mellitus), and medication (interferon, nonaspirin nonsteroidal anti-inflammation drugs, aspirin, statin, and antiviral therapy).

[b]Intervals of cDDDs in HBV cohort (28-42, 43-63, 64-119, and ≥ 120), HCV cohort (28-49, 50-84, 85-168, and ≥ 169), and HBV-HCV cohort (28-49, 50-84, 85-168, and ≥ 169).

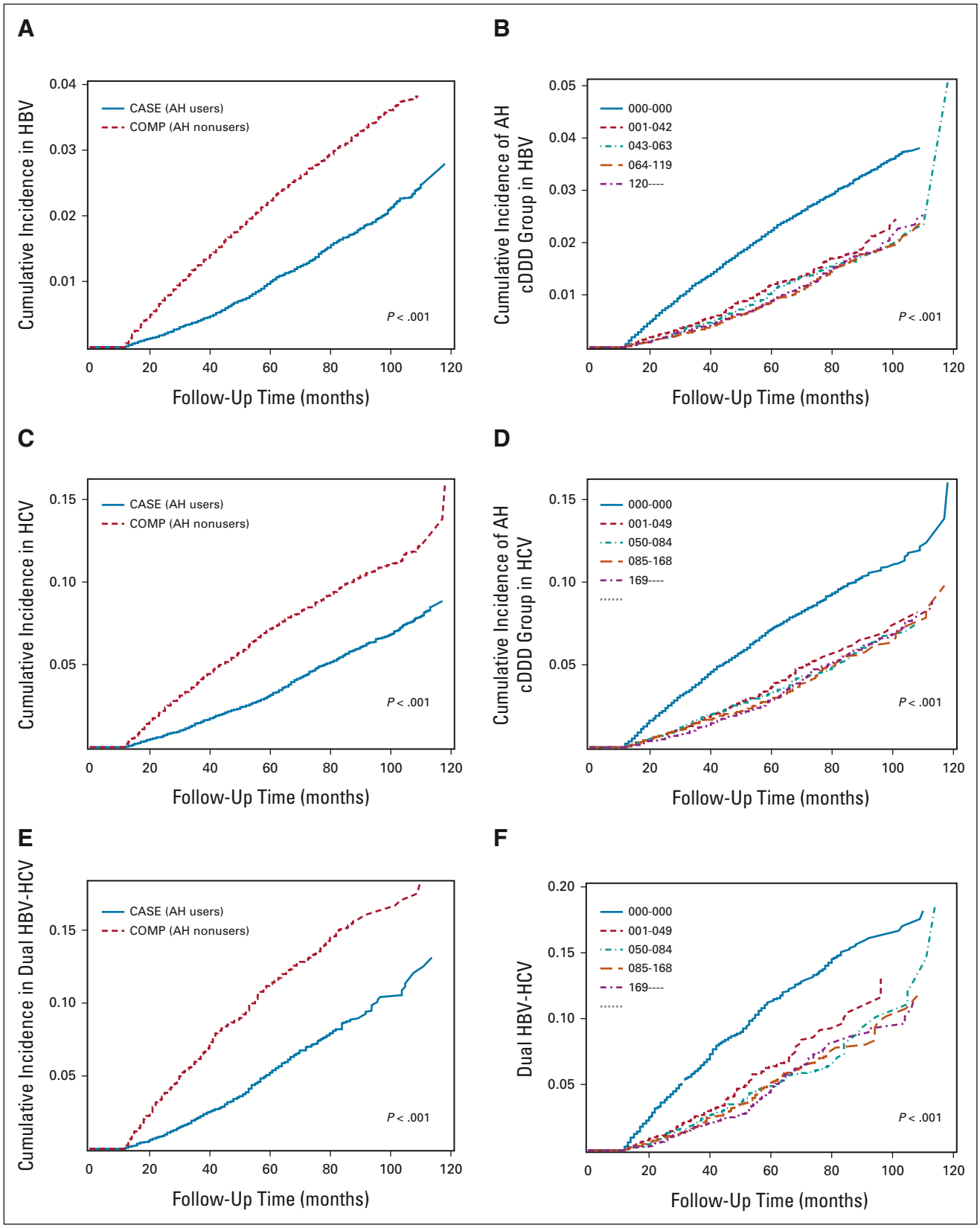

FIG 2. Cumulative incidence of hepatocellular carcinoma relative to cDDD of AH. (A) HBV cohort, (B) cDDD group in HBV cohort, (C) HCV cohort, (D) cDDD group in HCV cohort, (E) dual HBV-HCV cohort, and (F) cDDD group in dual HBV-HCV cohort. AH, antihistamine; cDDD, cumulative defined daily dose; HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 3. Association of Comorbidities and Concurrent Medications With Hepatocellular Carcinoma Risk

	HBV				HCV				Dual HBV-HCV			
	Univariate Model		Multivariate Model 1[a]		Univariate Model		Multivariate Model 1[a]		Univariate Model		Multivariate Model 1[a]	
Variable	Crude HR	95% CI	aHR	95% CI	Crude HR	95% CI	aHR	95% CI	Crude HR	95% CI	aHR	95% CI
AH use												
Nonuser (< 28 cDDDs)	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
User (≥ 28 cDDDs)	0.460***	0.430 to 0.493	0.489***	0.455 to 0.524	0.468***	0.436 to 0.502	0.484***	0.450 to 0.522	0.470***	0.420 to 0.526	0.469***	0.416 to 0.529
28-42 cDDDs[b]	0.508***	0.451 to 0.572	0.597***	0.530 to 0.674	0.495***	0.437 to 0.560	0.537***	0.474 to 0.608	0.546***	0.451 to 0.661	0.588***	0.485 to 0.713
43-63 cDDDs[b]	0.462***	0.407 to 0.524	0.528***	0.465 to 0.600	0.474***	0.417 to 0.538	0.518***	0.455 to 0.589	0.456***	0.371 to 0.560	0.514***	0.418 to 0.632
64-119 cDDDs[b]	0.425***	0.377 to 0.479	0.470***	0.416 to 0.531	0.452***	0.398 to 0.513	0.479***	0.420 to 0.545	0.444***	0.363 to 0.543	0.415***	0.339 to 0.509
≥ 120 cDDDs[b]	0.454***	0.405 to 0.508	0.407***	0.362 to 0.457	0.455***	0.405 to 0.511	0.425***	0.378 to 0.479	0.440***	0.363 to 0.533	0.394***	0.322 to 0.481
Sex												
Female	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Male	2.637***	2.418 to 2.876	2.345***	2.155 to 2.571	1.044	0.972 to 1.122	1.438***	1.337 to 1.548	1.074	0.950 to 1.215	1.470***	1.297 to 1.665
Age group, years												
18-30	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
31-40	2.311***	1.705 to 3.133	2.453***	1.811 to 3.324	3.794	0.894 to 16.103	3.854	0.903 to 16.45	1.884	0.652 to 5.441	1.868	0.647 to 5.391
41-50	6.609***	4.967 to 8.793	6.925***	5.202 to 9.221	21.51***	5.383 to 85.956	22.193***	5.519 to 89.25	7.315***	2.706 to 19.78	7.337***	2.714 to 19.83
51-60	14.608***	11.02 to 19.37	14.426***	10.85 to 19.18	62.062***	15.61 to 246.67	67.987***	16.99 to 272.1	16.936***	6.325 to 45.35	16.947***	6.316 to 45.47
61-70	23.007***	17.30 to 30.60	22.866***	17.09 to 30.60	121.591***	30.62 to 482.91	138.349***	34.57 to 553.7	29.613***	11.07 to 79.25	31.895***	11.88 to 85.67
71-80	32.236***	24.06 to 43.20	35.617***	26.37 to 48.11	162.856***	41.01 to 646.80	189.349***	47.26 to 758.6	39.242***	14.63 to 105.2	44.689***	16.58 to 120.4
> 80	33.218***	23.71 to 46.54	38.827***	27.34 to 55.13	130.812***	32.79 to 521.80	145.413***	36.12 to 585.5	27.424***	9.743 to 77.19	34.381***	12.12 to 97.49

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TABLE 3. Association of Comorbidities and Concurrent Medications With Hepatocellular Carcinoma Risk (continued)

	HBV				HCV				Dual HBV-HCV			
	Univariate Model		Multivariate Model 1[a]		Univariate Model		Multivariate Model 1[a]		Univariate Model		Multivariate Model 1[a]	
Variable	Crude HR	95% CI	aHR	95% CI	Crude HR	95% CI	aHR	95% CI	Crude HR	95% CI	aHR	95% CI
Comorbidity												
Cirrhosis	14.127***	13.10 to 15.23	3.107***	2.824 to 3.419	6.642***	6.135 to 7.190	4.069***	3.740 to 4.428	5.631***	4.979 to 6.369	3.137***	2.739 to 3.593
Nonalcoholic liver disease	0.598**	0.438 to 0.817	0.607**	0.447 to 0.825	0.815	0.604 to 1.100	1.028	0.767 to 1.378	0.586*	0.346 to 0.994	0.723	0.426 to 1.226
Alcoholic liver disease	1.936***	1.443 to 2.596	1.414*	1.047 to 1.909	1.028	0.752 to 1.405	1.449*	1.050 to 1.999	1.579*	1.088 to 2.294	2.112***	1.450 to 3.078
Hypertension	2.217***	2.066 to 2.380	1.208***	1.112 to 1.312	1.724***	1.607 to 1.850	1.107*	1.023 to 1.199	1.780*	1.583 to 2.002	1.176*	1.030 to 1.342
Chronic kidney disease	2.460***	2.002 to 3.024	1.237	0.996 to 1.537	1.076	0.897 to 1.290	0.801*	0.666 to 0.964	0.953	0.695 to 1.308	0.787	0.565 to 1.095
Hyperlipidemia	0.917	0.829 to 1.015	0.848**	0.760 to 0.947	0.693***	0.614 to 0.783	0.856*	0.753 to 0.973	0.807*	0.667 to 0.977	0.859	0.701 to 1.052
Diabetes mellitus	2.920***	2.702 to 3.155	1.672***	1.531 to 1.827	1.893***	1.753 to 2.044	1.567***	1.440 to 1.706	2.023***	1.781 to 2.297	1.574***	1.370 to 1.808
Medication												
Interferon	0.582	0.083 to 4.080	0.400	0.058 to 2.743	0.621	0.280 to 1.376	0.564	0.252 to 1.264	—	—	—	—
Nonaspirin NSAIDs	0.874***	0.818 to 0.934	0.740***	0.689 to 0.793	0.847***	0.789 to 0.908	0.732***	0.680 to 0.789	0.832**	0.743 to 0.931	0.724***	0.641 to 0.817
Aspirin	1.437***	1.321 to 1.562	0.848**	0.771 to 0.932	1.062	0.982 to 1.149	0.788***	0.723 to 0.859	1.161*	1.021 to 1.320	0.855*	0.741 to 0.986
Statin	0.781***	0.714 to 0.855	0.582***	0.526 to 0.645	0.451***	0.403 to 0.505	0.420***	0.372 to 0.474	0.590***	0.498 to 0.698	0.531***	0.443 to 0.638
Antiviral therapy	8.975***	8.412 to 9.576	5.768***	5.332 to 6.239	0.874**	0.802 to 0.951	1.219***	1.113 to 1.334	1.559***	1.385 to 1.755	1.645***	1.447 to 1.871

NOTE. $*P < .05$, $**P < .01$, $***P < .001$.

Abbreviations: AH, antihistamine; aHR, adjusted hazard ratio; cDDD, cumulative defined daily dose; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; NSAID, nonsteroidal anti-inflammation drug; Ref., reference.

[a]Multivariate model adjusted for sex, age, comorbidity (cirrhosis, nonalcoholic liver disease, alcoholic liver disease, hypertension, chronic kidney disease, hyperlipidemia, and diabetes mellitus), and medication (interferon, nonaspirin NSAIDs, aspirin, statin, and antiviral therapy).

[b]Intervals of cDDDs in HBV cohort (28-42, 43-63, 64-119, and ≥ 120), HCV cohort (28-49, 50-84, 85-168, and ≥ 169), and dual HBV-HCV cohort (28-49, 50-84, 85-168, and ≥ 169).

population). The Longitudinal Health Insurance Database, which is also referred to as the NHI Research Database, is managed by Taiwan's National Health Research Institute.[43]

After anonymizing the data to ensure patient privacy, we extracted the data (which included information on the patients' diagnosis, treatments, and drug use) for analysis. The Institutional Review Board of Taipei Medical University (TMU JIRB-N201908055) approved and granted a waiver of informed consent for this study, which was conducted per the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. This study also conforms to the Helsinki Declaration Guidelines.

Study Design and Participants

This retrospective cohort study was conducted using the Longitudinal Health Insurance Database. To ensure the validity and reliability of diagnoses, we only included adult patients who received HBV or HCV infection diagnoses (Appendix Table A1, online only) that were confirmed through three or more ambulatory care claims or in an inpatient setting. Patients were tracked from the date of initial diagnosis to the development of HCC (Appendix Table A1), their death, or the cohort exit date. We excluded patients who (1) were diagnosed with HCC within one year after HBV, HCV, or dual HBV-HCV was diagnosed, (2) were unknown sex or age, or younger than age 18 years, (3) were diagnosed with HCC within 1 year after index data, (4) had a follow-up duration of $<$ 1 year, and (5) were diagnosed with any form of cancer (Appendix Table A1) within 1 year before the start of the cohort entry date, which was designed to prevent other HCC-related metastases from influencing our results. The duration of follow-up was defined as 1 year after initial AH use or the cohort entry date. The incident of HCC was defined as the end point.

AH Exposure

AHs (Appendix Table A2, online only) are given for asthma,[44] allergic rhinitis,[45] medication allergies, environmental allergies, or symptoms caused viral infections, which include runny nose, itchy eyes, and pruritus. AHs are covered by Taiwan's NHI. We further collected information pertaining to drug type, dosage, route of administration, date of prescription, and total number of drug pills dispensed by the pharmacy. Because AH use might have occurred in separate years during the study period and because patients might have changed their drug use patterns over time, we treated AH use as a time-varying covariate in the Cox model. Cumulative dose was determined by multiplying the number of pills dispensed by the prescribed dose and dividing this value by the recorded days' supply. AH dosage was presented as the defined daily dose, which was established by the WHO as the average maintenance dose per day for a drug used for its main indication in adults. The calculation of cumulative defined daily dose (cDDD) means the sum of the daily prescribed dose. We defined $<$ 28 cDDDs as non-AH user to exclude occasional use of AH drugs. Among the eligible patients, AH use was indicated by cDDDs of $\geq$ 28. Furthermore, we divided the patients into four subgroups that were stratified by quartiles of cDDD (Appendix Table A3, online only).

Identification of Patients With HCC

The primary outcome was the occurrence of HCC, which diagnosis was confirmed by certification record in the Registry for Catastrophic Illness Patients.[46]

Comorbidities and Concomitant Medications

We determined potential confounders by (1) associating a given covariate with AH use on the basis of the literature and (2) determining the direct or indirect association with other conditions (such as comorbidities and concomitant medications). In accordance with the method used in another study,[47] we identified comorbidities on the basis of at least two diagnoses of a given disease made within 180 days before and after the cohort entry date; comorbidity codes are presented in the Appendix Table A1.

Statistical Analysis

Information pertaining to the patients' baseline characteristics, including age, sex, coexisting medical conditions, and AH doses, were collected. We categorized age in 10-year intervals. The baseline characteristics of AH users and nonusers were compared using the chi-squared test and *t* test for categorical variables and continuous variables, respectively; in addition, the Wilcoxon rank-sum test was applied to median values of distributions. The baseline was set as the cohort entry date. To understand the HCC risk of AH and non-AH users, we calculated incidence rates (IRs) and incidence rate ratios (IRRs) by using a formula and we estimated adjusted hazard ratios (aHRs) and 95% CIs by using Cox regression models to evaluate the occurrence of HCC among AH and non-AH users. The baseline information was used for exposure in model adjustment, during which we adjusted for sex, age, and the Charlson comorbidity index. Cumulative IRs of HCC were estimated using the Kaplan-Meier method and compared using the log-rank test.

All statistical analyses were performed using SAS for Windows version 9.4 software (SAS Institute, Cary, NC), and a two-sided *P* value of $<$ .05 was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Population

Figure 1 presents the study flow chart. In total, 1,077,982 patients with chronic HBV, HCV, or dual infections during the period from 2006 to 2015 were identified. After excluding patients (1) diagnosed with HCC within 1 year after HBV, HCV, or dual infections was diagnosed (n = 33,860),

(2) unknown sex or age, or younger than age 18 years (n = 14,506), (3) diagnosed with HCC within 1 year after index data (n = 8,485), (4) less than 1 year follow-up (n = 216,001), and (5) with cancer (n = 75,884), the eligible population (n = 729,246) was enrolled and segmented into the three following categories: (1) HBV cohort (n = 521,071), (2) HCV cohort (n = 169,159), and (3) dual HBV-HCV cohort (n = 39,016). After performing individual matching at a 1:1 ratio, the three cohorts were each segmented into AH-user and nonuser subgroups; the HBV cohort had 127,398 AH users and 127,398 AH nonusers, the HCV cohort had 40,428 AH users and 40,428 AH nonusers, and the dual HBV-HCV cohort had 8,661 AH users and 8,661 AH nonusers.

Table 1 presents the baseline characteristics of AH users and their matched controls. In the HBV cohort, the mean ages of patients in the AH-nonuser and AH-user groups were 47.08 years (standard deviation [SD], 13.34 years) and 47.09 years (SD, 13.37), respectively. In the HCV cohort, the mean ages of patients in the AH-nonuser and AH-user groups were 57.0 years (SD, 15.10) and 57.0 years (SD, 15.10), respectively. In the dual HBV-HCV cohort, the mean ages of patients in the AH-nonuser and AH-user groups were 53.97 years (SD, 14.19) and 53.98 years (SD, 14.19), respectively.

IRs, IRRs, and aHRs of HCC Among AH Users and Nonusers in Each Cohort

Table 2 presents the correlation between AH exposure and HCC development in each cohort.

In the HBV cohort, 1,191 and 2,443 events were observed in the AH-user and AH-nonuser groups, respectively, during the follow-up period. The IR of HCC was significantly lower in the AH-user group (198.35 per 100,000 person-years) than in the AH-nonuser group (426.03 per 100,000 person-years). Relative to the AH-nonuser group, a lower IRR of HCC was observed in the AH-user group (IRR, 0.466; 95% CI, 0.434 to 0.499). Furthermore, after we adjusted for age, sex, and comorbidities, in the HBV cohort, the risk of developing HCC was significantly lower in the AH-user group than in the AH-nonuser group, with aHR (0.489 [0.455 to 0.524]). In addition, we also observed a significantly lower IRR and aHR of HCC in the HCV-AH-user group (IRR, 0.488 [0.454 to 0.525]; aHR, 0.484 [0.450 to 0.522]) and in the dual-AH-user group (IRR, 0.489 [0.435 to 0.550]; aHR, 0.469 [0.416 to 0.529]) than in the AH-nonuser group, respectively.

A dose-response relationship between AH use and HCC risk was observed in the HBV cohort; relative to AH nonusers (< 28 cDDDs), the aHRs were 0.597, 0.528, 0.470, and 0.407 for AH users with cDDDs of 28-42, 43-63, 64-119, and ≥ 120, respectively. Additionally, there was also a dose-response relationship between AH use and the risk of HCC in the HCV and dual HBV-HCV cohorts.

Our Kaplan-Meier analyses revealed that HBV-AH users had a lower risk of developing HCC (log-rank test, $P < .001$) than HBV-AH nonusers (Fig 2A). Even when the patients were stratified by the cDDD of AH, a similar trend was observed (Fig 2B). The aforementioned trend was also observed in the HCV (log-rank test, $P < .001$; Fig 2C) and dual HBV-HCV (log-rank test, $P < .001$; Fig 2E) cohorts across all cDDD groups (Figs 2D and 2F).

Associated of Comorbidities and Concurrent Medications With HCC Risk

Table 3 shows the association of HCC with concurrent medications and comorbidities.

In the HBV cohort, HCC risk increased with age (with the aHR of patients age 18-30 years used as a reference) and was also higher in male patients (aHR, 2.345; 95% CI, 2.155 to 2.571) relative to female patients. Comorbidities such as cirrhosis (3.107 [2.824 to 3.419]), diabetes mellitus (1.672 [1.531 to 1.827]), alcoholic liver disease (1.414 [1.047 to 1.909]), and hypertension (1.208 [1.112 to 1.312]) were also associated with a higher risk of HCC development. Furthermore, the use of concurrent medications, such as nonaspirin nonsteroidal anti-inflammation drugs (NSAIDs; 0.740 [0.689 to 0.793]) and statin (0.582 [0.526 to 0.645]), was associated with a lower HCC risk.

In the HCV cohort, male patients (1.438 [1.337 to 1.548]), cirrhosis (4.069 [3.740 to 4.428]), diabetes mellitus (1.567 [1.440 to 1.706]), and hypertension (1.107 [1.023 to 1.199]) were also associated with a higher risk of HCC development. The use of nonaspirin NSAIDs (0.732 [0.680 to 0.789]) and statin (0.420 [0.372 to 0.474]) was associated with a lower risk of HCC.

Similar results were found in the dual infection cohort, except alcoholic liver disease was associated with a higher risk of HCC development in the dual cohort.

DISCUSSION

Per our literature review, this is the first nationwide population-based study to investigate the relationship between AH use and HCC risk in viral hepatitis. The results indicated that patients with HBV, HCV, or dual virus infections who used AH had an approximately two-fold lower risk of HCC when compared with patients who did not use AH. To the best of our knowledge, our study is the first to report a dose-response relationship between AH use and HCC risk in patients with HBV, HCV, or dual virus infections after controlling for confounders.

Cancer often results from chronic inflammation, and anti-inflammatory medications are therefore candidates for repurposing as drugs for cancer therapy. Fritz et al[48] discovered an association between the use of specific AHs and improved breast cancer survival; other studies have reported similar results for nonlocalized cancer, non–small-cell lung cancer, and ovarian cancer, and research has indicated that

some AHs that are normally used to alleviate allergic reactions may also have antitumor effects.[3] Therefore, the repurposing of AH is a means of meeting this need.

The mechanism through which AH use reduces HCC risk is poorly understood. However, several mechanisms have been proposed and investigated. Research has indicated that AH use can inhibit the growth of liver cancer and be regarded as a new cancer treatment.[49] The underlying mechanism may involve the blocking of cell cycle progression through the activation of mitogen-activated protein kinases,[38] and the combined use of other drugs such as vitamin D[50] and thalidomide[35] can enhance the effect of AHs on HCC. AHs have even been linked to significant improvements in the survival outcomes of patients with advanced HCC.[36] In addition, AHs can meaningfully inhibit the infection of HCV genotypes 1b and 2a in chimeric mice engrafted with primary human hepatocytes.[41] From a microscopic perspective, AHs can increase the calcium-ion concentration in hepatic malignant cells.[51] In our previous cell model experiments, we observed that the administration of deptropine could inhibit the combination of autophagosome and lysosome and, ultimately, induce hepatoma cell death.[39] Although no mechanism have been discussed in the aforementioned studies, AH is nevertheless believed to have a role in immunoregulation. Moreover, unlike other anti-inflammatory drugs, AH can induce hepatoma cell death.

The findings of some clinical studies correspond to our finding that AH use may reduce HCC risk. The combined use of cyproheptadine and thalidomide was reported to have resulted in the disappearance of liver tumors and lung metastases.[35] Another clinical study also demonstrated that the combined use of sorafenib and cyproheptadine increased patients' mean survival time from 4.8 to 11 months and their progression-free survival from 1.7 to 7.5 months.[36] Relative to traditional therapies, the use of only cyproheptadine significantly improved survival rates in patients with HCC.[37]

In this study, statin use was observed to be associated with a lower risk of HCC in the HBV, HCV, and dual-infection cohorts; this finding corresponds with that reported by Tsan et al[52,53] regarding the protective effect of statin use on such cohorts. A recent study investigated statins as anticancer agents by examining preclinical evidence on their antiproliferative, proapoptotic, anti-invasive, and radiosensitizing properties.[54] The statin-induced inhibition of HMG-CoA reductase interferes with the rate-limiting step in the mevalonate pathway, and this effect may inhibit tumor initiation, growth, and metastasis.[55]

In addition, in this study, the effect of aspirin on HCC risk remained inconclusive after it was assessed using different models that were applied to all cohorts—although a nationwide study of patients with chronic viral hepatitis in Sweden indicated that the use of low-dose aspirin is associated with a significantly lower risk of HCC and lower liver-related mortality relative to the absence of aspirin use.[56] Therefore, the association between aspirin and HCC risk requires further clarification.

Furthermore, our study indicated that NSAIDs exhibited mild protective effects against HCC. The death of hepatocytes in patients with HBV, HCV, or dual infections may cause these hepatocytes to undergo carcinogenesis during the process of continuous apoptosis and regeneration. The use of anti-inflammatory drugs has not been proven to slow down carcinogenic progress, reduce cancer incidence, or block the immune system to let the virus infection or HCC worsen. These facts about these drugs seem to hold despite being contradictory. Therefore, the effects of anti-inflammatory drugs, which include NSAIDs, disease-modifying antirheumatic drugs, steroids, and AHs, ought to be separately discussed. By contrast, older adults and men were observed to have a greater risk of HCC in the HBV, HCV, and dual-infection cohorts.

Tsan et al[52] revealed that anti-HBV treatment aided the prevention of HCC; this finding is consistent with that reported in our study. Our results indicated that antiviral therapy was associated with a higher risk of HCC in the HBV and dual HBV-HCV cohorts. The results for the HCV cohort, which were obtained using univariate and multivariate models, were inconclusive. We should consider the state of and payment model entailed in Taiwan's NHI. Unless they choose to undergo self-funded treatments, patients with virus-related hepatitis ought to receive antiviral therapy when they have elevated levels of liver enzymes or cirrhosis; in reality, only patients with severe conditions (and not patients with mild or no symptoms) receive antiviral drugs.

The advantages of this study included its large sample size, large validation cohort, and its long-term verification of medication information. However, it also had some limitations. First, although the NHI Administration routinely and randomly checks patient charts to ensure the quality of claims from medical institutions, the possibility of miscoding or misclassification cannot be completely ruled out. Second, the relationship between disease activity and the severity of chronic viral hepatitis was not analyzed. Third, several unmeasured HCC-related confounders (including body mass index, smoking habit, alcohol intake, and use of other over-the-counter drugs) were not included in our database. Fourth, we were unable to contact patients directly about their use of AH because their identities were anonymized. We presumed that all patients adhered to their prescribed medication regimens; thus, the actual ingested dosage might have been overestimated because some degree of nonadherence is usually present. Finally, laboratory and clinical data were not readily accessible through the administrative database. In the future, prospective studies can verify whether the activity and severity of chronic viral hepatitis or clinical biomarkers affect HCC risk.

In conclusion, AH use may reduce HCC risk in patients with HBV, HCV, or dual infections in a dose-dependent manner. AH use could be a potential adjuvant strategy for preventing HCC in patients with HBV, HCV, or dual infections. Further research on the underlying mechanisms is required.

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EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

The data sets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

H1-Antihistamines Reduce the Risk of Hepatocellular Carcinoma in Patients With Hepatitis B Virus, Hepatitis C Virus, or Dual Hepatitis B Virus-Hepatitis C Virus Infection

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

APPENDIX

TABLE A1. ICD-9 Codes of Disease Diagnosis and Comorbidities

Variable	ICD-9 Code
Disease diagnosis	
HBV	070.2, 070.3, and V02.61
HCV	070.41, 070.44, 070.51, 070.54, and V02.62
HCC	155.0 and 155.2
Comorbidity	
Cirrhosis	571, 571.2, 571.5, and 571.6
Nonalcoholic liver disease	571.8
Alcoholic liver disease	571.0, 571.1, 571.2, 571.3
Hypertension	401-405, 642
Chronic kidney disease	585
Hyperlipidemia	272
Diabetes mellitus	250, 648
Cancer	140-208

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD-9, International Classification of Diseases, Ninth Revision.

TABLE A2. ATC Code of AHs

ATC Code	AH Drugs
R06AA	Aminoalkyl ethers[57]
R06AA02	Diphenhydramine
R06AA04	Clemastine
R06AA07	Diphenylpyraline
R06AA08	Carbinoxamine
R06AA09	Doxylamine
R06AA52	Diphenhydramine, combinations (not included)
R06AA57	Diphenylpyraline, combinations (not included)
R06AB	Substituted alkylamines[58]
R06AB01	Brompheniramine
R06AB02	Dexchlorpheniramine
R06AB03	Dimetindene
R06AB04	Chlorpheniramine
R06AB54	Chlorpheniramine, combinations (not included)
R06AD	Phenothiazine derivatives[59]
R06AD01	Alimemazine
R06AD02	Promethazine
R06AD03	Thiethylperazine
R06AD07	Mequitazine
R06AE	Piperazine derivatives[60]
R06AE01	Buclizine
R06AE03	Cyclizine
R06AE04	Chlorcyclizine
R06AE05	Meclozine
R06AE06	Oxatomide
R06AE07	Cetirizine
R06AE09	Levocetirizine
R06AE51	Buclizine, combinations (not included)
R06AE55	Meclozine, combinations (not included)
R06AK	Combinations of AHs
R06AK	Combinations of AHs (not included)
R06AX	Other AHs for systemic use[61]
R06AX01	Bamipine
R06AX02	Cyproheptadine
R06AX04	Phenindamine
R06AX07	Triprolidine
R06AX09	Azatadine
R06AX11	Astemizole
R06AX12	Terfenadine
R06AX13	Loratadine
R06AX15	Mebhydrolin
R06AX17	Ketotifen
R06AX18	Acrivastine
R06AX22	Ebastine
R06AX25	Mizolastine
R06AX26	Fexofenadine
R06AX27	Desloratadine
R06AX91	Clemizole HCl (no cDDD data, rarely used, not included)

Abbreviations: AH, antihistamine; ATC, anatomical therapeutic chemical system of medications; cDDD, cumulative defined daily dose.

TABLE A3. Antihistamine Stratified by Quartiles of Cumulative Defined Daily Dose

Cohort	Stratified Dose
HBV cohort	28-42, 43-63, 64-119, and ≥ 120
HCV cohort	28-49, 50-84, 85-168, and ≥ 169
Dual HBV-HCV	28-49, 50-84, 85-168, and ≥ 169

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.