

Association Between Acid-Suppressive Agents' Use and Risk of Hepatocellular Carcinoma

Dose-Response:
An International Journal
April-June 2020:1-8
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DOI: 10.1177/1559325820907530
journals.sagepub.com/home/dos



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Abstract

Background: Acid-suppressive agents (ASAs), which are mostly used in patients with upper gastrointestinal diseases (UGIDs), may influence the risk of hepatocellular carcinoma (HCC).

Methods: A population-based retrospective cohort study was conducted. Patients with UGID who used ASAs and those who did not receive ASAs were identified. Patients without UGIDs were randomly selected and matched (comparison group). All groups were followed up for 6 years. A Cox proportional hazard model was used to estimate the risk of HCC among the different groups.

Results: Patients with UGID who used ASAs had a significantly elevated HCC risk (adjusted hazard ratio [HR] 1.53; 95% confidence interval [CI], 1.32-1.76) compared to those who did not use ASAs. Patients with UGID who used more than 540 defined daily doses of ASAs had a significantly higher risk of HCC (adjusted HR 2.04; 95% CI, 1.62-2.58). Moreover, the dose effect on HCC risk exhibited a significant increasing trend ($P < .01$). Furthermore, patients with UGID who did not use ASAs had a significantly elevated HCC risk (adjusted HR 1.94; 95% CI, 1.59-2.36) compared to the comparison group.

Conclusion: The use of ASAs increased the risk of HCC in patients with UGIDs, and the effect of ASAs was dose dependent. In addition, UGIDs alone increased the risk of HCC.

Keywords

acid-suppressive agents, proton pump inhibitors, histamine 2 receptor antagonists, hepatocellular carcinoma, dose-dependent

Introduction

The most commonly used acid-suppressive agents (ASAs) to treat acid-related upper gastrointestinal (GI) diseases (UGIDs), such as gastroesophageal reflux disease and peptic ulcer disease (PUD), are proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H₂RAs).^{1,2} Both PPIs and H₂RAs are generally known for their safety and efficacy for UGIDs.³ However, there is emerging evidence indicating that long-term use of PPIs and H₂RAs is associated with concerns of bacterial overgrowth, hypergastrinemia, and malignancies.⁴⁻⁶

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer.⁷ In 2012, liver cancer was the seventh most frequently occurring cancer and the third leading cause of cancer-related deaths worldwide,⁸ whereas it was the third most common cancer and the second leading cause of cancer-related deaths in Taiwan.^{9,10}

Currently, there are several potential mechanisms suggesting that PPIs and H₂RAs might be related to HCC. Hypoacidity caused by PPIs and/or H₂RAs may lead to bacterial overgrowth

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Received 19 July 2019; received revised 1 January 2020; accepted 16 January 2020

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and facilitate formation of *N*-nitroso compounds, lipopolysaccharide (LPS), and deoxycholic acid (DCA).¹¹⁻¹⁶ *N*-Nitroso compounds, LPS, and DCA were all shown to be associated with the development of HCC.¹⁵⁻²⁴ In addition, hypergastrinemia induced by PPIs and/or H₂RAs may be associated with HCC. Gastrin was found to be related to GI malignancies.^{4,14,25,26} Furthermore, gastrin receptors are expressed in tumor sections of patients with HCC, and gastrin was shown to stimulate the growth of liver cells.^{27,28} Moreover, the growth-stimulating effect is inhibited by the gastrin receptor antagonists such as the Parke-Davis compounds PD 135 and PD 138.²⁸ However, very few studies have examined the influence of the use of ASAs, such as PPIs and/or H₂RAs, on the risk of HCC, despite the common use of these medications in patients with UGID and the potential mechanism indicating the impact of these medications on the risk of HCC. Therefore, the aim of this study is to explore the impacts of ASAs on the risk of HCC in patients with UGID.

Method

Data Sources

The Longitudinal Health Insurance Database 2000 (LHID2000), one of the data subsets of the National Health Insurance (NHI) Research Database (NHIRD),²⁹ was used to conduct a population-based retrospective nationwide cohort study. The NHIRD is a large computerized database derived from the nationwide NHI program in Taiwan and is maintained by the National Health Research Institutes (NHRI) for research purposes. There are approximately 23.75 million individuals in the NHIRD, which contains the original registration and claims data for reimbursement of the single-payer NHI program, and 1 million individuals randomly sampled from the 2000 Registry for Beneficiaries (ID) constitute the LHID2000. There was no significant difference in the number of birth per year, the age distribution, or the gender distribution between patients in the LHID2000 and the original NHIRD.

Data in the NHIRD were deidentified before being sent to the NHRI for database construction and further scrambled before being released to researchers. Researchers obtain no information that could potentially violate the privacy of patients and therefore informed consent was not required. This study was exempted from full review by the joint institutional review board of Taipei Medical University (TMU-JIRB: N201511002).

Study Population

Patients diagnosed with at least 2 episodes of UGIDs (*International Classification of Diseases*, ninth revision [*ICD-9*] codes 530-536) between January 1, 2001, and December 31, 2005, were included from the LHID2000, with an exclusion of those who were aged ≤ 18 years. Patients with UGID receiving ASAs (PPIs and/or H₂RAs) were identified, and those who had the first administration of ASAs after the UGID diagnosis date

were recruited. Patients who had received PPIs and/or H₂RAs for less than 90 days within 365 days after the index date (first administration of ASAs) or those with any cancers (*ICD-9* codes 140-209) before the index date were excluded (study group I). In addition, patients with UGID who did not use PPIs or H₂RAs were identified, and those with any cancers before the UGID diagnosis date were excluded as well (study group II). Patients without UGIDs between January 1, 2001, and December 31, 2005, were identified from the LHID2000, and those who had used PPIs and/or H₂RAs were excluded. These patients were then randomly selected, matched (at a 1:1 ratio) to study group II patients by age, gender, and index year, and those with any cancers before the reference date (the first date of any records in the LHID2000) were excluded (comparison group). All groups were followed up for 6 years.

Primary Outcomes

The primary purpose of the study is to ascertain whether ASAs are associated with an increased risk of HCC (*ICD* codes 155.0 and 155.1) in patients with UGID. For the primary outcome, we evaluated the risk of occurrence of HCC during the follow-up period in the study groups compared to the comparison group.

Secondary Outcomes

We also endeavored to analyze the dose-response relationship between the risk of HCC and the use of ASAs. In order to calculate and compare the cumulative numbers of doses of different drugs, the concept of the defined daily dose (DDD) was applied. The anatomical therapeutic chemical (ATC)/DDD system, a universal drug measurement system, was used to measure the exposure to PPIs and/or H₂RAs.³⁰ The ATC system classifies drugs, and every medication with an ATC code is assigned a DDD as the unit of drug measurement. The DDD is defined as the assumed average daily maintenance dose for a medication used for its main indication in adults.^{30,31} The secondary outcome was an analysis of hazard ratios (HRs) of HCC in subgroups of patients only receiving PPIs or H₂RAs during the follow-up period.

Potential Risk Factors

The potential risk factors included age, gender, viral hepatitis (*ICD-9* codes 070.0-070.9, V02.61, and V02.62), chronic liver disease and cirrhosis (*ICD-9* code 571), alcohol abuse (*ICD-9* code 305.0), obesity (*ICD-9* code 278.0), diabetes mellitus (*ICD-9* code 250), schistosomiasis parasitic infection (*ICD-9* code 120), tobacco use disorder (*ICD-9* code 305.1), statin use, thiazolidinedione use, and metformin use.

Statistical Analyses

Pearson χ^2 test and Student *t* test were used to evaluate differences in baseline characteristics of all groups. A Cox proportional hazard regression model was used to estimate the risk of HCC among different groups, after adjusting for potential risk

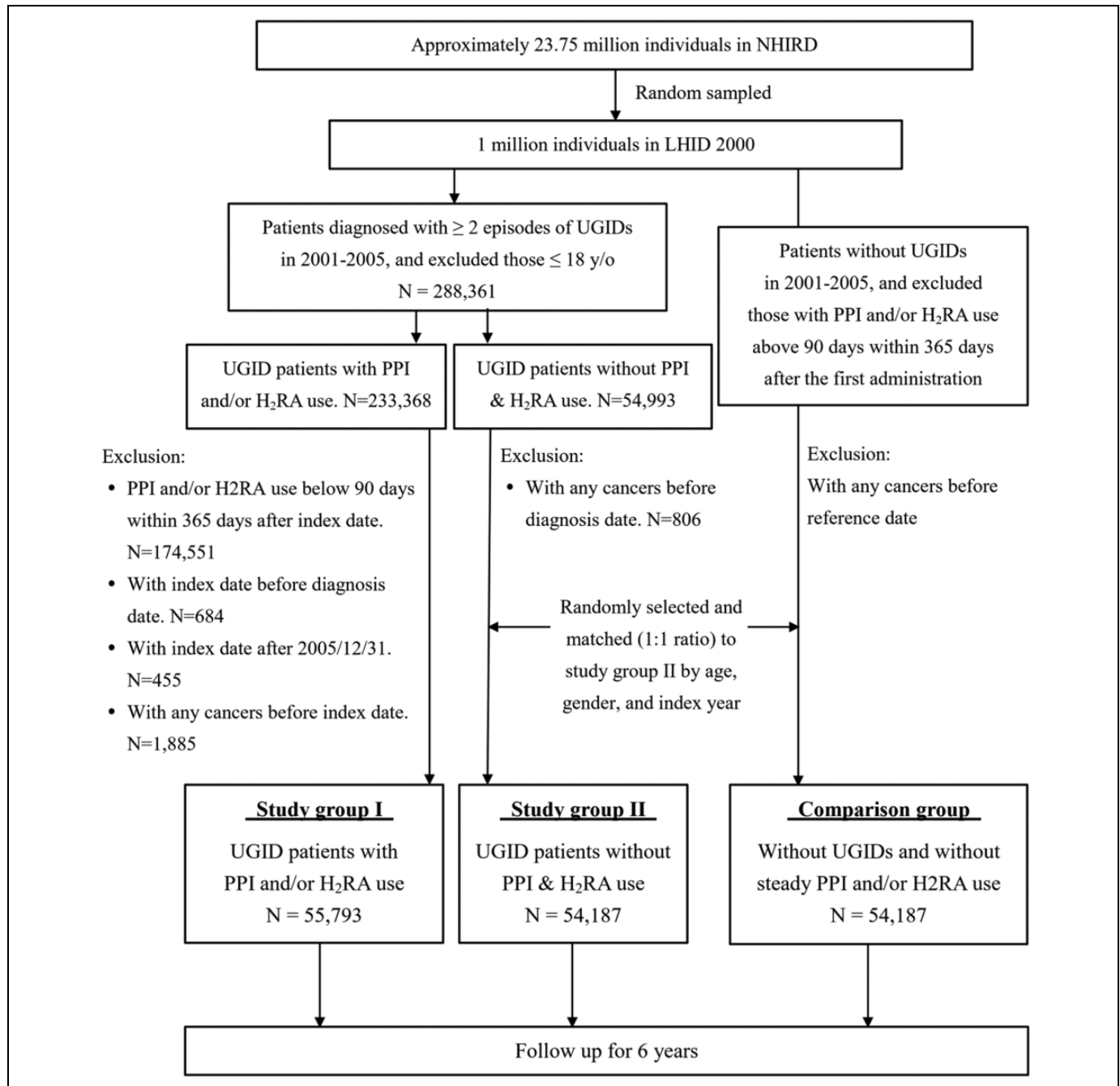


Figure 1. Flowchart of study design. Index date is the first administration date of acid-suppressive agents (PPIs/H₂RAs), and diagnosis date is the first diagnosis date of UGIDs. H₂RA indicates histamine 2 receptor antagonist; LHID, Longitudinal Health Insurance Database; NHIRD, National Health Insurance Research Database; PPI, proton pump inhibitor; UGID, upper gastrointestinal disease; y/o, years old.

factors of HCC. The time of HCC occurrence and the cumulative incidence of HCC of the study group II and comparison group were assessed by the Kaplan-Meier method, and differences between the various groups were analyzed by a log-rank test. All significance tests were 2 sided, and *P* values of <.05 were considered significant. SAS version 9.1 software (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

Results

From the LHID2000 data subset of the NHIRD, 288 361 patients diagnosed with at least 2 episodes of UGIDs in 2001 to 2005 were included (Figure 1). After exclusion and matching, there were 55 793 patients with UGID who had used ASAs (study group I) and 54 187 patients with UGID who had not received ASAs (study group II). The comparison group consisted of 54 187 patients without UGIDs and who did not use

Table 1. Baseline Characteristics of the Comparison and Study Groups.

Variables	Study Group (Patients With UGID)		Comparison Group	P Value ^a	P Value ^b
	With PPI and/or H ₂ RA Use (Study Group I), N = 55 793	Without PPI or H ₂ RA Use (Study Group II), N = 54 187	Without UGIDs and Without PPI and/or H ₂ RA Use, N = 54 187		
Age, years (mean ± SD)	53.33 ± 15.27	45.90 ± 18.35	45.90 ± 18.35	<.001	1
Gender/male, n (%)	25 558 (45.81)	26 081 (48.13)	26 081 (48.13)	<.001	1
Viral hepatitis, n (%)	7440 (13.35)	3013 (5.56)	2539 (4.69)	<.001	<0.001
Chronic liver disease and cirrhosis, n (%)	17 427 (31.4)	8316 (15.35)	7221 (13.33)	<.001	<0.001
Alcohol abuse, n (%)	564 (1.01)	212 (0.39)	205 (0.38)	<.01	0.73
Obesity, n (%)	1108 (1.99)	710 (1.31)	670 (1.24)	.07	0.28
Diabetes mellitus, n (%)	13 579 (24.34)	6183 (11.41)	6232 (11.50)	.32	0.64
Parasite infection, schistosomiasis, n (%)	2 (0.003)	2 (0.003)	0	.86	0.16
Tobacco use disorder, n (%)	2014 (3.61)	1010 (1.86)	1001 (1.85)	.05	0.84
Statin use, n (%)	15 211 (27.26)	6284 (11.61)	6205 (11.45)	<.001	0.45
Thiazolidinedione use, n (%)	3632 (6.51)	1573 (2.90)	1399 (2.58)	.59	<0.01
Metformin use, n (%)	7707 (13.81)	3516 (6.49)	3799 (7.01)	.72	<0.01

Abbreviations: H₂RA, histamine 2 receptor antagonist; PPI, proton pump inhibitor; SD, standard deviation; UGID, upper gastrointestinal disease.

^aStudy group I versus study group II patients with UGID.

^bStudy group II patients with UGID versus comparison group.

Table 2. Hepatocellular Carcinoma (HCC) Risk and Time of Occurrence Among the Comparison Group, Study Group II, and Study Group I (Patients With UGID with Proton Pump Inhibitor [PPI] and/or Histamine 2 Receptor Antagonist [H₂RA] Use).

Result	Study Group (Patients With UGID)		Comparison Group
	With PPI and/or H ₂ RA Use (Study Group I), N = 55 793	Without PPI or H ₂ RA Use (Study Group II), N = 54 187	Without UGIDs and Without PPI and/or H ₂ RA Use, N = 54 187
HCC, n (%)	600 (1.08)	299 (0.55)	149 (0.27)
Incidence rate (per 10 000 patients) (95% CI)	107.57 (99.15-116.45)	55.18 (49.12-61.78)	27.50 (23.26-32.28)
Crude HR (95% CI)	1.95 (1.71-2.24) ^a	1	—
Adjusted HR ^b (95% CI)	1.53 (1.32-1.76) ^a	1	—
Crude HR (95% CI)		2.01 (1.65-2.45) ^a	1
Adjusted HR ^b (95% CI)		1.94 (1.59-2.36) ^a	1

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation; UGID, upper gastrointestinal disease.

^aP < .001.

^bAdjusted for age, gender, viral hepatitis, chronic liver disease, cirrhosis, alcohol abuse, obesity, diabetes mellitus, parasite infection (schistosomiasis), tobacco use disorder, statin use, thiazolidinedione use, and metformin use.

ASAs (comparison group). Baseline characteristics of these groups are presented in Table 1.

During the follow-up period, there were 600 (1.08%) new HCC cases in study group I, 299 (0.55%) in study group II, and 149 (0.27%) in comparison group, and the risks of HCC occurrence were compared among different groups (Table 2). After adjustment, patients with UGID who used ASAs (PPIs and/or H₂RAs) had a significantly increased risk of HCC (adjusted HR 1.53; 95% confidence interval [CI], 1.32-1.76) compared to those who did not use them. Compared to patients without UGIDs and who did not use ASAs (comparison group), the risk of HCC was also significantly higher in patients with UGID who did not use ASAs (adjusted HR 1.94; 95% CI, 1.59-2.36).

For patients with UGID who only used PPIs, the risk of HCC was also significantly higher compared to those who used

no PPIs or H₂RAs (adjusted HR 2.73; 95% CI, 1.56-4.78, P < .001). However, for those who only used H₂RAs, the adjusted HR was 0.77 (95% CI, 0.58-1.00), and the risk of HCC was not significantly higher compared to those who used neither PPIs nor H₂RAs (Table 3).

When the exposure to ASAs was divided into 4 groups (<180 DDDs, 180-360 DDDs, 360-540 DDDs, and >540 DDDs), the risk of HCC was all significantly higher than that of study group 2, and P for trend was <.01 (Table 4). In addition, the result of Kaplan-Meier analysis, which patients with UGID who used no ASAs (study group II) had a higher cumulative incidence of HCC than patients without UGIDs and who used no ASAs (comparison group) is shown in Figure 2. The log-rank test of the Kaplan-Meier analysis was also significant (P < .001).

Table 3. Hepatocellular Carcinoma (HCC) Risk and Time of Occurrence Among the Comparison Group, Study Group II, and Patients With Upper Gastrointestinal Disease (UGID) Only With Proton Pump Inhibitor (PPI) Use or Only With Histamine 2 Receptor Antagonist (H₂RA) Use.

Result	Patients With UGID		
	Only With PPI Use, N = 700	Only With H ₂ RA Use, N = 13 776	Without PPI or H ₂ RA Use (I), N = 54 187
HCC, n (%)	13 (1.86)	68 (0.49)	299 (0.55)
Incidence rate (per 10 000 patients) (95% CI)	185.71 (99.25-315.48)	49.36 (38.35-62.54)	55.18 (49.12-61.78)
Crude HR (95% CI)	3.38 (1.94-5.89) ^a	0.89 (0.69-1.16)	1
Adjusted HR ^b (95% CI)	2.73 (1.564.78) ^a	0.77 (0.581.00)	1

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation.

^aP < .001.

^bAdjusted for age, gender, viral hepatitis, chronic liver disease, cirrhosis, alcohol abuse, obesity, diabetes mellitus, parasite infection (schistosomiasis), tobacco use disorder, statin use, thiazolidinedione use, and metformin use.

Table 4. Effects of Proton Pump Inhibitor (PPI) and/or Histamine 2 Receptor Antagonist (H₂RA) Exposure on the Hepatocellular Carcinoma (HCC) Risk and Time of Occurrence Among Patients With Upper Gastrointestinal Disease (UGID).

Result	Patients With UGID				
	Without PPI and H ₂ RA Use (Study Group II) N = 54 187	With PPI and/or H ₂ RA Use (I)			
		<180 DDDs N = 26 944	180-360 DDDs N = 14 658	360-540 DDDs N = 5986	>540 DDDs N = 8205
HCC, n (%)	299 (0.55)	225 (0.84)	166 (1.13)	89 (1.49)	120 (1.46)
Incidence rate (per 10 000 patients) (95% CI)	55.18 (49.12-61.78)	83.51 (72.99-95.10)	113.25 (96.75-131.72)	148.68 (119.57-182.65)	146.25 (121.40-174.63)
Crude HR (95% CI)	1	1.51 (1.27-1.81) ^a	2.06 (1.70-2.48) ^a	2.70 (2.13-3.43) ^a	2.66 (2.15-3.28) ^a
Adjusted HR ^b (95% CI)	1	1.26 (1.05-1.51) ^c	1.55 (1.27-1.90) ^a	1.98 (1.54-2.55) ^a	2.04 (1.62-2.58) ^a

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; SD, standard deviation.

^aP < .001.

^bAdjusted for age, gender, viral hepatitis, chronic liver disease, cirrhosis, alcohol abuse, obesity, diabetes mellitus, parasite infection (schistosomiasis), tobacco use disorder, statin use, thiazolidinedione use, and metformin use.

^cP < .01.

Discussion

In this large population-based cohort study, the use of ASAs, that is, PPIs and/or H₂RAs, significantly increased the risk of HCC in patients with UGID, and this increased HCC risk was dose dependent. To our best knowledge, very little research has studied the relationship between ASAs and HCC, and the mechanism is still unclear. It is possible that the hypoacidity resulting from ASAs might cause bacterial overgrowth and hypergastrinemia. Hypoacidity may lead to bacterial overgrowth and facilitate formation of *N*-nitroso compounds, LPS, and DCA.¹¹⁻¹⁶ *N*-Nitroso compounds, LPS, and DCA are all known to be associated with the development of HCC.¹⁵⁻²⁴ In addition, hypergastrinemia induced by ASAs may be associated with HCC. Gastrin receptors are expressed in tumor sections of patients with HCC, and gastrin was shown to stimulate

the growth of liver cells.^{27,28} Moreover, bacterial overgrowth and hypergastrinemia could both be related to HCC, as mentioned above.

In this study, patients with UGID who used only PPIs had a bigger risk of HCC than those who used PPIs and/or H₂RAs (study group I) compared to those who used neither PPIs nor H₂RAs. In addition, patients with UGID who used only H₂RAs were not associated with the risk of HCC compared to those who used neither PPIs nor H₂RAs. This is possibly because PPIs are more potent in acid inhibition than H₂RAs, so the extents of consequent bacterial overgrowth and hypergastrinemia were also greater.^{11,12,25} Besides, H₂RAs were proposed to have an anticancer effect. In a hepatoma cell line study, it was demonstrated that histamine binding to H₂ receptor can inhibit interleukin (IL)-6 binding to cancer cells, which leads to less

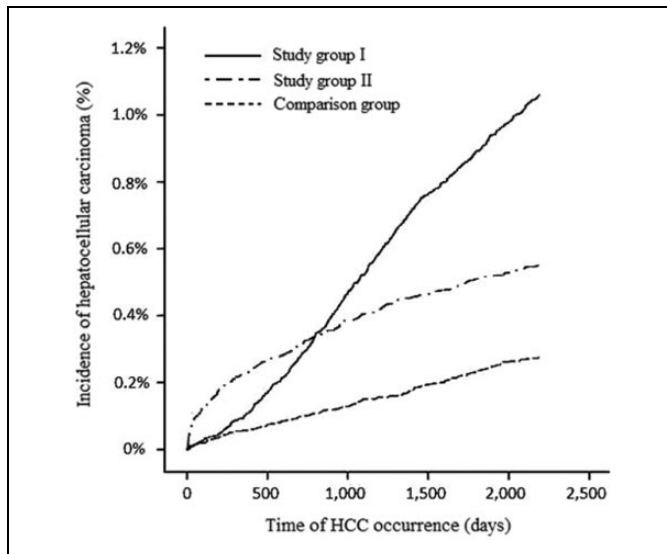


Figure 2. Kaplan-Meier curve of the cumulative incidence of hepatocellular carcinoma among the comparison group, study group I, and study group II. Study group I comprises patients with upper gastrointestinal disease (UGID) with proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H₂RA) use; study group II comprises patients with UGID without PPI or H₂RA use; comparison group, without UGIDs and without PPI and/or H₂RA use. $P < .001$ by the log-rank test. HCC indicates hepatocellular carcinoma.

IL-6 expression and reduces inhibition of cancer cell growth.³¹ Some clinical studies revealed that the use of the H₂RA, cimetidine, prolonged survival in patients with gastric cancer and colorectal cancer.³² A cohort study in Taiwan showed that exposure to a higher cumulative dose (≥ 360 DDD) of H₂RAs might be associated with a decreased risk of non-small cell lung cancer in type 2 diabetic patients.³³ Moreover, it is plausible that patients with UGID who only use a higher cumulative dose of H₂RAs might have a significantly decreased risk of HCC. Tran et al³⁴ found that the use of PPIs was associated with an increased liver cancer risk (adjusted odds ratio [OR] 1.80, 95% CI, 1.34-2.41; adjusted HR 1.99, 95% CI, 1.34-2.94) and slight evidence of an association with H₂RA use (adjusted OR 1.21, 95% CI, 0.84-1.76; adjusted HR 1.70, 95% CI, 0.82-3.53). Their results are similar to our findings. However, our study patients all had a UGID diagnosis and long-term use of ASAs, that is, PPIs and/or H₂RAs. We could ensure patients' ASA use was reasonable and show the cause-consequence relationship between ASAs and the risk of HCC. In addition, a case-control study explored the relationship between the use of PPIs and/or H₂RAs and the risk of HCC and reported no association between PPI use and HCC. Moreover, there was a significant positive association between H₂RA use and the risk of HCC.³⁵ That result is opposite to the results of this study. However, PPI use and H₂RA use were only defined as "ever used" in that study, possibly underestimating the impact of PPI use and H₂RA use on the risk of HCC. Besides, it was a case-control study, and a logistic regression was used to analyze the risk of HCC. As a

result, it is not likely to show cause-consequence relationships of PPIs and/or H₂RAs with the risk of HCC.

As mentioned above, the underlying indication for the use of PPIs and/or H₂RAs, that is, UGIDs, alone may increase the risk of HCC. In this study, UGIDs alone significantly increased the risk of HCC. The relationship between UGIDs and HCC has seldom been studied. Nevertheless, *Helicobacter pylori* (*Hp*) infection, the most common cause of PUP, was found to be related to HCC.³⁶⁻⁴¹ *Helicobacter pylori* was detected in liver tissues of patients with HCC and found to be hepatotoxic.⁴²⁻⁴⁴ *Helicobacter pylori* can also produce LPS, which promotes adhesion and invasion of liver tumors and stimulates tumor growth.^{45,46} In addition, *Hp* infection in the oxyntic area, causing atrophy, leads to reduced gastric acid secretion and significant consequent hypergastrinemia.^{47,48} Partial reversion of hypergastrinemia and Enterochromaffin-like cells hyperplasia was found in patients with atrophic body gastritis after eradication of *Hp*.⁴⁹ On the other hand, *Hp* infection in the antrum only results in slight hypergastrinemia, increased gastric acid secretion, and possibly subsequent bacterial overgrowth and hypergastrinemia.^{47,48} In a meta-analysis, *Hp* infection was positively associated with the risk of HCC (summary OR 13.63; 95% CI, 7.90-23.49).

In this study, the use of PPIs and/or H₂RAs increased the risk of HCC, and it was mainly caused by PPIs. *Helicobacter pylori* was shown to augment the acid-inhibiting effect of PPIs.⁵⁰ In addition, in patients under long-term PPI therapy, the overgrowth of non-*Hp* bacteria was found to be more significant in patients with *Hp* infection compared to those without.

There are several strengths in this study. This is the first study to investigate the relationship between the use of ASAs and the risk of HCC in patients with UGIDs, the first study to explore the dose effect of ASAs on the risk of HCC, and the first study to analyze the cumulative incidence among patients with UGID with PPI and/or H₂RA use, without PPI and/or H₂RA use, and patients without UGIDs and who did not use PPIs and/or H₂RAs. In addition, the study population was selected from the NHIRD, so it is a large population-based cohort study with rather good generalizability. Moreover, the definitions of the use of ASAs and patients with UGID were very clear, thus reducing the classification bias. The potential confounders were deliberately selected, thereby decreasing interference by other factors. In addition, the follow-up period was rather long, reducing the possibility of underestimating or overestimating the occurrence of HCC.

There are some limitations of this study. The study information is restricted to recorded data of the NHIRD, but there is no evidence suggesting that there was a systematic difference among the various groups. The accuracy of the coding of diagnoses is not known; however, patients with UGID in this study were defined as having been diagnosed at least twice with UGIDs, so that possible bias was reduced. Information on compliance and the availability of over-the-counter PPIs and/or H₂RAs could not be collected; nevertheless, the definition of PPI and/or H₂RA use was the use of PPIs and/or

H₂RAs for more than 90 days within 365 days after the first administration, and so all of these patients exhibited long-term use of PPIs and/or H₂RAs to treat UGIDs. The cause–consequence relationship between ASAs and the risk of HCC was greatly increased.

In conclusion, the use of ASAs (PPIs and/or H₂RAs) increased the risk of HCC in patients with UGIDs, and the impact was dose dependent. In addition, UGIDs alone were found to increase the risk of HCC. More clinical and/or animal studies are warranted to confirm these results.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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