

Hydroxychloroquine Reduced the Risk of Hepatocellular Carcinoma in Patients with Hepatitis C Virus infection: A Retrospective Cohort Study

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Abstract

Purpose

Hydroxychloroquine (HCQ) exerts anticancer effects through anti-inflammatory, autophagy-related, and non-autophagy-related mechanisms. This study investigated the association between HCQ use and risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C virus (HCV) infection.

Methods

We enrolled patients with HCV infection from Taiwan's National Health Insurance Research Database, covering the period from January 1, 2006, to December 31, 2016. Kaplan–Meier analysis and Cox proportional hazards regression were used to analyze the HCC risk in HCQ users and non-users. We evaluated the association between HCC risk, concurrent medication use, and comorbidities.

Results

We included 139,263 patients with a newly diagnosed HCV infection. During the follow-up period, 1037 patients developed HCC. In the HCQ user group ($n = 1598$), 62 patients had HCC, whereas 975 of the 15,980 HCQ non-users developed HCC. Patients with chronic HCV infection who used HCQ had a significantly lower risk of HCC than those who did not (adjusted hazard ratio [aHR], 0.68; 95% Confidence interval [CI], 0.51–0.92). No dose–response relationship was observed between the HCQ user and non-user groups. The use of concurrent medications, such as antihistamines (aHR, 0.74; 95% CI, 0.59–0.93), statins (aHR, 0.38; 95% CI, 0.32–0.46), nonsteroidal anti-inflammatory drugs (aHR, 0.60; 95% CI, 0.48–0.76), and aspirin (aHR, 0.82; 95% CI, 0.72–0.94), was associated with a lower risk of HCC.

Conclusion

HCQ use may reduce the risk of HCC in patients with HCV infection. These results provide key insights into the potential benefits of HCQ use in preventing HCC in patients with chronic HCV infection.

1 Introduction

Drug repositioning has gained considerable attention in recent years. This approach involves identifying new therapeutic uses for existing drugs. Drug development is a lengthy and costly process, with considerable uncertainty and attrition rates.(1) Thus, drug repositioning can accelerate drug development and reduce risks because these drugs have already been subjected to batteries in clinical trials and have been demonstrated to be safe through extensive clinical use. The pharmacokinetics, chemical composition, and toxicology of these drugs are well understood, and can shorten the time required for market approval.(2) In addition, repurposed drugs are often cheap and may be more readily

accepted by the market.(3, 4) Many existing drugs have been successfully repositioned for uses beyond their original indications. For example, aspirin, which was initially developed as an analgesic, is now widely used for the prevention of cardiovascular disease.(5, 6) Similarly, thalidomide, originally an antiemetic that was banned due to its teratogenic effects, has been repurposed for the treatment of leprosy and multiple myeloma.(7)

Hydroxychloroquine (HCQ) is an analog of chloroquine (CQ), which was originally derived from *Cinchona calisaya* and first used to treat malaria.(8, 9) HCQ has since been repurposed for various conditions, including autoimmune diseases such as rheumatoid arthritis(10) and systemic lupus erythematosus.(11, 12) During the COVID-19 pandemic, HCQ was used to treat patients with COVID-19 because a clinical trial found that HCQ significantly reduced viral load and shortened the duration of infection.(13) However, subsequent clinical trials have demonstrated no significant reduction in mortality or improvement in clinical outcomes following HCQ use.(14, 15) Previous studies have suggested that HCQ possesses anticancer properties and major underlying mechanisms involve both autophagy and non-autophagy-related pathways.(16, 17) In terms of autophagy, HCQ contains a basic amine that increases lysosomal pH, disrupting the fusion of autophagosomes and lysosomes and thereby impairing autophagic function.(18) In addition, HCQ may activate apoptosis and necroptosis as part of its non-autophagy-related anticancer mechanisms.(16)

Hepatitis C virus (HCV) is a single-stranded RNA virus that was first identified in 1989.(19) Seven genotypes of HCV genotypes were identified.(20) More than 70 million people worldwide have chronic HCV infection, and up to 20% of those with chronic infection develop complications, such as liver cirrhosis and hepatocellular carcinoma (HCC).(21) Chronic HCV infection accounts for 30% of all HCC cases and is associated with a higher risk of liver cirrhosis than hepatitis B virus (HBV) infection.(22) In Taiwan, HCV infection is the leading cause of hepatocellular carcinoma (HCC).(23) Recent studies have indicated that autophagy plays a key role in several liver diseases, including HBV or HCV infection and HCC.(24) Disruption of autophagy proteins is associated with an increased risk of spontaneous HCC in mice.(25) In addition, studies have demonstrated that the expression and activity of autophagy-related genes is decreased in HCC cells.(26, 27) In patients with HCC who have undergone liver transplantation, the use of autophagy activators improves post-transplant survival.(28) These findings support the role of autophagy as a protective mechanism against cancer development.(29) However, the effect of HCQ on HCC risk in patients with chronic HCV infection remains unclear. The present study investigated the association between HCQ use and risk of HCC in patients with chronic HCV infection.

2 Materials and methods

2.1 Data collection

Since its launch in 1995, Taiwan National Health Insurance (NHI) system has served as the primary health insurance provider on the island, covering over 99.5% of the population. The Taiwan National Health Insurance Research Database (NHIRD) contains the medical records of almost every resident of

the Taiwanese population for almost three decades. The NHIRD contains complete medical information including textual and imaging data.

We used the NHIRD to collect and analyze cohort data from January 1, 2006, to December 31, 2016. Patient diagnoses and drug histories were also analyzed. The Institutional Review Board of Taipei Medical University approved this study (approval number: N202005078). Informed consent was not required because the data were anonymized and were used only for research purposes.

The *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* and *International Classification of Diseases, Tenth Revision (ICD-10)* were used to identify the disease diagnoses. The Anatomical Therapeutic Chemical (ATC) classification system was used to identify medication use in the cohort. HCV infection was identified using the following codes: *ICD-9-CM* 070.41, 070.44, 070.51, 070.54, and V02.62, and *ICD-10* B18.2 and B19.2. HCC was identified using *the ICD-9-CM* 155.0, 155.2, and *ICD-10* C22.0. The codes for the diagnosis of other comorbidities are listed in the **appendix**. HCQ use was identified using ATC code P01BA02.

2.2 Study design

Patients with newly diagnosed HCV infection were defined as those with no history of HCV infection. After the initial diagnosis, patients were required to have either two outpatient department visits or one hospital admission record with an HCV infection diagnosis within one year of the first diagnosis. The primary outcome of this study was HCC diagnosis, as recorded in the patients' medical records. Patients were followed up until the diagnosis of HCC, the end of the follow-up period, or death, whichever occurred first. We excluded patients with unknown sex or age, were aged < 18 years, had a duration between HCQ initiation and HCC occurrence of < 12 months, had a duration between cohort entry and HCC occurrence of < 12 months, had a follow-up period of < 12 months, received a diagnosis of HCC before 2006 or before a new HBV or HCV diagnosis, had used HCQ before 2006 or before a new diagnosis of HBV or HCV infection, had a diagnosis of other cancers (*ICD-9-CM* codes 104–208), and had coinfection with both HBV and HCV.

2.3 Exposure to HCQ

HCQ has been widely used to treat autoimmune diseases and is covered by the Taiwan NHI system. From the NHIRD, we collected information on the drug dosage, prescription date, cumulative drug amount, and administration route. However, because HCQ use may have varied across different years in this cohort study and patients might have adjusted their medication patterns, we treated HCQ use as a time-varying covariate in the Cox model. To standardize drug exposure, we used the defined daily dose (DDD) system established by the World Health Organization, which represents the average dose required to maintain therapeutic efficacy in adults. The DDD for HCQ was approximately 0.5 g per day. HCQ use was defined as a cumulative DDD (cDDD) of ≥ 28 days. Patients were further categorized into three subgroups on the basis of their cDDD: $28 \leq \text{cDDD} < 86.82$, $86.82 \leq \text{cDDD} < 263.18$, and $\text{cDDD} \geq 263.18$. In addition, we examined the association between the average cDDD per year of HCQ use and the risk of

HCC by dividing patients into three subgroups: average cDDD/year < 19.89, $19.89 \leq$ average cDDD/year < 61.25, and average cDDD/year $\geq$ 61.25.

2.4 Comorbidities and concurrent medications

Patients with chronic HCV infection who use HCQ may also have other systemic diseases or may take additional medications. Thus, we examined the association between comorbidities, concurrent medication use, and HCC risk. Comorbidities were defined as the presence of at least two diagnoses of a given disease made within 180 days of the cohort entry date.⁽³⁰⁾ The comorbidities assessed included liver cirrhosis (*ICD-9-CM* 571.5, *ICD-10* K74.0, K74.60, and K74.69), non-alcoholic liver disease (*ICD-9-CM* 571.8; *ICD-10* K76.0), alcoholic liver disease (*ICD-9-CM* 571.0, 571.1, 571.2, 571.3; *ICD-10* K70), hypertension (*ICD-9-CM* 401–405, 642; *ICD-10* I10–I13, I15), chronic kidney disease (*ICD-9-CM* 585; *ICD-10* N18), hyperlipidemia (*ICD-9-CM* 272; *ICD-10* E78), and diabetes mellitus (*ICD-9-CM* 250; *ICD-10* E10–E14). Concurrent medication use was defined as any record of medication use within 180 days of the cohort entry date. Concurrent medications included antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, statins, systemic glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs (bDMARDs), and antiviral agents. The ATC codes for these medications are provided in the appendix.

2.5 Statistical analysis

Differences in baseline characteristics between HCQ users and non-users were analyzed using the Student's *t*-test for continuous variables and Pearson's chi-square test for categorical variables. To analyze the risk of HCC in HCQ users and non-users, we calculated the incidence rate (IR) and IR ratio for the unadjusted risk of HCC using a predefined formula. Poisson distribution and test-based methods were used to calculate confidence intervals (CIs) for IR. Adjusted hazard ratios (aHRs) and 95% CIs were estimated using Cox proportional hazards regression to evaluate the occurrence of HCC in HCQ users and non-users. The Kaplan–Meier method was used to estimate the cumulative event rate of HCC in HCQ users and non-users, and comparisons were made using the log-rank test.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as a two-sided *p*-value < 0.05.

3 Results

3.1 Baseline characteristics of HCQ users and nonusers

From January 1, 2006, to December 31, 2016, a total of 276,031 patients with a new diagnosis of HCV infection were identified in the NHIRD. Figure 1 shows the flowchart of patient recruitment and exclusion. Patients were excluded for the following reasons: unknown sex or age (*n* = 922), age < 18 years (*n* = 648), duration between HCQ initiation and HCC occurrence < 12 months (*n* = 29), duration between cohort entry and HCC occurrence < 12 months (*n* = 15,477), follow-up period < 12 months (*n* = 78,296), diagnosis of HCC before 2006 or before a new diagnosis of HBV or HCV infection (*n* = 3954), use of HCQ before

2006 or before a new diagnosis of HBV or HCV infection ($n = 4294$), diagnosis of other cancers ($n = 40,086$), and coinfection with both HBV and HCV ($n = 46,927$). After excluding these patients, 139,263 patients with newly diagnosed HCV infection remained in the study. Of these, 2285 patients were HCQ users and 136,978 were HCQ nonusers. Subsequently, 1:10 individual matching was conducted based on age ($\pm$ year), sex, and the index year. After matching, we included 1598 and 15,980 patients in the HCQ and HCQ non-user groups, respectively. Table 1 shows the baseline characteristics of each group. The mean age of patients in the HCQ user and non-user groups was 60.60 years (standard deviation [SD], 11.07). Patients were also categorized into three subgroups based on their cDDD: 511 patients in the $28 \leq \text{cDDD} < 86.82$ subgroup, 553 in the $86.82 \leq \text{cDDD} < 263.18$, and 534 in the $\text{cDDD} \geq 263.18$ subgroup. In addition, patients were divided into three subgroups on the basis of average cDDD per year: 532 patients in the average cDDD/year < 19.89 subgroup, 533 in the $19.89 \leq \text{average cDDD/year} < 61.25$ subgroup, and 533 in the average cDDD/year ≥ 61.25 subgroup. The median follow-up duration was 4.99 (SD, 3.65) years in the HCQ user group and 4.61 (SD, 3.57) years in the HCQ nonuser group.

Table 1
Baseline Characteristics of the HCV Cohort

HCV cohort					
	HCQ Users N = 1598		HCQ Nonusers N = 15,980		p Value
	N	%	N	%	
Gender					
Female	1,163	72.78	11,630	72.78	1
Male	435	27.22	4,350	27.22	
AGE Group (Years)					1
< 40	72	4.51	720	4.51	
41–50	214	13.39	2,140	13.39	
51–60	510	31.91	5,100	31.91	
61–70	477	29.85	4,770	29.85	
> 70	325	20.34	3,250	20.34	
Mean ± SD	60.60 ± 11.07		60.60 ± 11.07		1
Median (IQR)	61	53	61	53	1
HCQ Use					
Nonusers (< 28 cDDD _s)	0	0	15,980	0	
Users	1,598	100	0	0	
cDDD _s (tertile)					
28–86.82	511	31.98			
86.82–263.18	553	34.61			
≥ 263.18	534	33.42			
Mean (SD)	266.99 ± 310.81				
*Autoimmune diseases were not included.					
≤ 3: According to the regulations of the Ministry of Health and Welfare, any data in which a variable is less than 3 cannot be directly presented to avoid revealing identifiable personal information. Such data must be indicated as “≤3’.”					

HCV cohort					
average cDDDs per year (tertile)					
< 19.89	532	33.29			
19.89–61.25	533	33.35			
≥ 61.25	533	33.35			
Mean (SD)	55.90 ± 55.58				
Follow-Up Time (year)					
Median (IQR)	4.99	3.65	4.61	3.57	< .0001
ARD					
Rheumatoid arthritis	573	35.86	53	0.33	
Systemic lupus erythematosus	149	9.32	3	0.02	
Primary Sjögren’s syndrome	629	39.36	53	0.33	
Other autoimmune disease	177	11.08	10	0.06	
Other*	404	25.28	15,868	99.30	
Comorbidity					
Liver cirrhosis	122	7.63	1,302	8.15	0.4735
Nonalcoholic liver disease	26	1.63	175	1.10	0.0565
Alcoholic liver disease	22	1.38	198	1.24	0.6369
Hypertension	663	41.49	6,150	38.49	0.0188
Chronic kidney disease	113	7.07	921	5.76	0.0341
Hyperlipidemia	263	16.46	2,408	15.07	0.1402
Diabetes mellitus	271	16.96	2,927	18.32	0.1797
Medication					
Antihistamines	1,527	95.56	14,697	91.97	< .0001
Non-aspirin NSAIDs	1,554	97.25	14,940	93.49	< .0001
*Autoimmune diseases were not included.					
≤ 3: According to the regulations of the Ministry of Health and Welfare, any data in which a variable is less than 3 cannot be directly presented to avoid revealing identifiable personal information. Such data must be indicated as “≤3’.”					

HCV cohort					
Aspirin	717	44.87	5,763	36.06	< .0001
Statins	437	27.35	4,472	27.98	0.5876
Systemic glucocorticoids	1,439	90.05	10,884	68.11	< .0001
DMARD					
Azathioprine	203	12.7	44	0.28	< .0001
Cyclophosphamide	27	1.69	13	0.08	< .0001
Cyclosporine	100	6.26	61	0.38	< .0001
Leflunamide	78	4.88	18	0.11	< .0001
Methotrexate	301	18.84	83	0.52	< .0001
Mycophenolate mofetil	7	0.44	73	0.46	0.9153
Sulfasalazine	400	25.03	125	0.78	< .0001
bDMARDs					
TNF- α antagonist	45	2.82	9	0.06	< .0001
Rituxumab	≤ 3		≤ 3		< .0001
Tofacitinib	≤ 3		≤ 3		< .0001
Antiviral agent					
Interferon	200	12.52	1,603	10.03	0.0018
Ribavirin	201	12.58	1,603	10.03	0.0014
*Autoimmune diseases were not included.					
≤ 3 : According to the regulations of the Ministry of Health and Welfare, any data in which a variable is less than 3 cannot be directly presented to avoid revealing identifiable personal information. Such data must be indicated as " ≤ 3 ."					

3.2 IRs, IRRs, and aHRs of HCC in HCQ users and nonusers

Table 2 presents the correlation between HCQ exposure and the development of HCC. Of the 15,980 HCQ nonusers in the HCV cohort, 975 had an HCC diagnosis. In contrast, of the 1598 HCQ users in the HCV cohort, 62 had an HCC diagnosis. A total of 1037 patients had an HCC diagnosis in the HCV cohort were diagnosed with HCC during the follow-up period. The IR of HCC in the HCQ user group (734.3 per 100,000 person-years) was significantly lower than that in the HCQ non-user group (1229.8 per 100,000 person-years). Furthermore, the crude HR of HCC in the HCQ user group was lower than that in the HCQ non-user group (crude HR, 0.59; 95% CI, 0.46–0.76). After adjustment for age, sex, and comorbidities, the

aHR was 0.68 (95% CI, 0.51–0.92). This result indicates that the HCQ user group had a significantly lower risk of HCC than the HCQ non-user group. To investigate the dose–response relationship between HCQ use and HCC risk, we divided patients into three subgroups based on their cDDD and average cDDD per year. The aHRs were 0.78 (95% CI, 0.51–1.20), 0.79 (95% CI, 0.50–1.25), and 0.48 (95% CI, 0.29–0.81) in the $28 \leq \text{cDDD} < 86.82$, $86.82 \leq \text{cDDD} < 263.18$, and $\text{cDDD} > 263.18$ subgroups, respectively, compared with the nonuser group. Furthermore, the aHRs were 0.52 (95% CI, 0.32–0.83), 0.76 (95% CI, 0.49–1.19), and 0.87 (95% CI, 0.54–1.39) in the average cDDD /year < 19.89 , $19.89 \leq \text{average cDDD/year} < 61.25$, and average cDDD/year > 61.25 subgroups, respectively, compared with the nonuser group. These results indicated the absence of a dose–response relationship between HCQ use and HCC risk.

Table 2
IRs and HRs of HCC in the HCV Cohort Based on Different HCQ Doses

	Events	Person Years	Incidence Rate	Crude HR	95% CI for crude HR	Adjusted HR [#]	95% CI for Adjusted HR
HCV cohort							
Nonusers (< 28 cDDDd)	975	79284.1	1229.8	Ref.		Ref.	
Users (≥ 28 cDDDd)	62	8443.5	734.3	0.59 ^{***}	0.46–0.76	0.68 [*]	0.51–0.92
cDDDd							
28–86.82	23	2653.76	866.7	0.70	0.46–1.06	0.78	0.51–1.20
86.82–263.18	22	2711.82	811.26	0.66	0.43–1.01	0.79	0.50–1.25
≥ 263.18	17	3077.93	552.32	0.44 [*]	0.27–0.71	0.48 [*]	0.29–0.81
average cDDDd per year							
< 19.89	18	3305.66	544.52	0.43 [*]	0.27–0.68	0.52 [*]	0.32–0.83
19.89–61.25	22	2636.06	834.58	0.68	0.45–1.04	0.76	0.49–1.19
≥ 61.25	22	2501.79	879.37	0.72	0.47–1.10	0.87	0.54–1.39
*p < 0.05, **p < 0.001, ***p < 0.0001							
# The multivariate model was adjusted for sex, age, comorbidities (liver cirrhosis, non-alcoholic liver disease, alcoholic liver disease, hypertension, chronic kidney disease, hyperlipidemia, and diabetes mellitus), and medication (antihistamines, non-aspirin NSAIDs, aspirin, statins, systemic glucocorticoids, DMARDs, bDMARDs, and antiviral agents).							

3.3 Comparison of cumulative event rate of HCC between the HCQ user and nonuser groups

Figure 2 presents a comparison of the cumulative incidence of HCC between the HCQ users and non-users. The Kaplan–Meier method revealed a significantly lower incidence of HCC events in the HCQ user group than in the non-user group (log-rank test, $p < 0.01$), and this difference became pronounced within the first year of follow-up and persisted throughout the study period.

3.4 Association of comorbidities and concurrent medication use with HCC risk

Table 3 presents the association between comorbidities, concurrent medication use, and HCC risk. Men were at a higher risk of HCC than women (aHR, 1.55; 95% CI, 1.36–1.78). The risk of HCC was higher in older patients and lower in younger patients when determined using the 51–60 year age group as the reference. aHRs for patients aged 1.82, 2.26, 0.41, and 0.08 for patients aged 61–70, 71–80, 41–50, and < 40 years, respectively, when compared with those aged 51–60 years. A higher HCC risk was associated with comorbidities of liver cirrhosis (aHR, 4.8; 95% CI, 4.16–5.52), hypertension (aHR, 1.21; 95% CI, 1.06–1.39), and diabetes mellitus (aHR, 1.62; 95% CI, 1.4–1.88). In addition, the use of concurrent medications, namely H1-antihistamines (aHR, 0.74; 95% CI, 0.59–0.93), NSAIDs (aHR, 0.60; 95% CI, 0.48–0.76), and statins (aHR, 0.38; 95% CI, 0.32–0.46), was associated with a lower risk of HCC.

4 Discussion

To the best of our knowledge, this is the first study to use a population-based database to examine the relationship between HCQ use and HCC risk in patients with chronic HCV infection. Our results indicate that patients with chronic HCV infection who used HCQ had a significantly lower risk of HCC than those who did not use HCQ.

Autophagy is a cellular metabolic process in which intracellular organelles(31) proteins, and pathogens are recycled, providing new energy sources for the cell. This process plays a crucial role in both physiological and pathophysiological conditions, particularly cell survival.(32) Under stressful conditions such as starvation, hypoxia, hyperthermia, and toxin exposure, autophagy is activated in mammalian cells, including cancer cells. A recent study has reported that autophagy plays a dual role in cancer development.(33) In the early stages of cancer, autophagy acts as a tumor suppressor by inducing apoptosis.(34) However, in the late stages of cancer, autophagy can protect the cancer cells from treatment. Thus, autophagy inhibitors or activators may serve as potential therapeutic agents for cancer treatment.(35)

CQ and its analog HCQ, along with other autophagy inhibitors, enhance the effects of anticancer therapies.(17) CQ and HCQ are weakly basic compounds that, upon entering lysosomes, increase lysosomal pH, thereby reducing lysosomal function. This disruption hinders the fusion of lysosomes with autophagosomes, a critical step in the formation of autolysosomes during autophagy.(36, 37)

Previous studies have indicated that CQ and HCQ exhibit antitumor mechanisms in addition to their role in autophagy. First, both CQ and HCQ can induce apoptosis. Kim et al. demonstrated that CQ activated the p53 pathway and suppressed glioma cell growth by inducing apoptosis in vitro and in vivo in an orthotopic (U87MG) human glioblastoma mouse model.(38) In human HeLa cells treated with HCQ, lysosomal membrane permeabilization was observed, along with increased lysosomal volume, cathepsin B release, and signs of apoptosis.(39) Second, CQ and HCQ have immunomodulatory properties. The Toll-like receptor (TLR) signaling cascade is a key pathway in the immune response. HCQ can inhibit the

phenotypic and functional maturation of dendritic cells by increasing the pH of acidic organelles. This increase in pH inhibits endosomal TLR activation and blocks TLR9 and TLR7 signaling.(40, 41) Studies have demonstrated that TLR9 is associated with increased cell proliferation, malignancy, and metastasis.(42, 43)

Previous studies have reported on the use of HCQ in cancer therapy in various contexts.(44) HCQ has demonstrated efficacy in cancer therapy, both in vitro and in vivo, as monotherapy(45) and in combination with chemotherapy,(46) radiation therapy,(47) monoclonal antibodies, immune checkpoint therapy, and surgery.(48)

Briceno et al. found that patients with glioblastoma treated with conventional methods plus CQ had a significantly longer survival than those treated with only conventional methods.(49) Triple-negative breast cancer (TNBC) is associated with poor prognosis due to its high rate of local recurrence and distal metastasis. This phenomenon is partly attributed to the high proportion of CD44⁺/CD24^{-/low} cancer stem cells present in TNBC tumors.(50) Cancer stem cells are responsible for tumor initiation and self-renewal. Although conventional treatments may eliminate the bulk of the tumor, these stem cells can survive and cause recurrence.(51) Liang et al. demonstrated that HCQ affects cancer stem cells by inhibiting autophagy, causing mitochondrial structural damage and impairing DNA repair. When HCQ was combined with carboplatin, carboplatin-induced autophagy was inhibited, resulting in decreased tumor growth in carboplatin-resistant breast cancer cells.(52) This finding suggests that combining HCQ with chemotherapy may be a promising treatment strategy for TNBC.

Sorafenib is an effective and widely used targeted therapy for patients with advanced stage HCC.(53, 54) However, some patients develop resistance to sorafenib after an initial response, potentially due to epigenetics, transport processes, regulated cell death, and the tumor microenvironment.(55) Previous studies have reported that TLRs such as TLR9 are overexpressed in HCC cells, promoting proliferation and reducing apoptosis. Chen et al. reported that, in sorafenib-resistant HCC cells, treatment with a combination of HCQ and sorafenib, both in vitro and in vivo, reduced the expression of TLR9 and cancer stem cell genes.(56, 57) The HCQ–sorafenib combination enhances treatment efficacy in HCC, offering a potential strategy to overcome sorafenib resistance.(57, 58)

HBV-induced HCC progression was faster in mice with defective autophagy (due to *Beclin-1* disruption) than in mice with normal autophagy function.(25) Autophagy activity may affect tumor aggressiveness and prognosis. In human HCC cell lines, the expression of the autophagy-related gene *Beclin 1* decreased and that of the anti-apoptotic gene *Bcl-xL* increased when compared with a normal hepatic cell line. In addition, the most aggressive malignant or recurrent HCC cell line exhibits a considerably low level of autophagy. *Beclin-1* expression significantly correlated with disease-free and overall survival in the Bcl-xL⁺ group.(26)

In a previous study involving liver transplantation, 2491 and 12,167 recipients received transplants for HCC and non-HCC reasons, respectively. After treatment with rapamycin, an autophagy activator, for at

least six months after transplantation, HCC recipients experienced prolonged survival. In contrast, non-HCC recipients tended to have shorter survival rates following rapamycin therapy. These results indicate a cancer-specific benefit of rapamycin therapy.(28)

The results of the present study revealed that, in addition to HCQ, antihistamines, statins, NSAIDs, and aspirin were associated with a lower risk of HCC. Inflammation plays a crucial role in cancer development, because the inflammatory microenvironment promotes cell proliferation and increases the risk of neoplasia.(59) Thus, anti-inflammatory drugs can be used for cancer treatment and prevention. Numerous studies have indicated that anti-inflammatory drugs exert anticancer effects by altering the tumor microenvironment, increasing apoptosis, and enhancing chemosensitivity.(60) In liver cells, chronic inflammation and the associated tissue damage and remodeling processes lead to immunosuppression, which inactivates the antitumor immune response as HCC develops or metastasizes.(61) In their cohort study, Shen et al. found that in patients with HBV, HCV, or dual infections, the use of antihistamines reduced the risk of HCC by approximately 2-fold when compared with no use of antihistamines.(62)

Studies have investigated the potential anticancer effects of NSAIDs owing to their anti-inflammatory properties.(63, 64) A study examining the effects of ibuprofen on tumor growth reported that ibuprofen inhibited the proliferation of mouse and human colorectal tumors by 40–82%. In addition, fewer liver metastases were observed in a colorectal cancer mouse model. When combined with 5-fluorouracil or irinotecan, the ibuprofen-treated group had smaller tumor sizes than the non-ibuprofen group.(65) NSAIDs have also been associated with a decreased risk of other cancers such as breast cancer,(66) prostate cancer, and HCC.(63, 67)

Aspirin is a well-known case of drug repositioning and has been repurposed for use in cancer treatment and prevention.(68) The proposed mechanisms underlying the anticancer effects of aspirin include modulation of signal transcription and mitochondrial functions, and inhibition of enzymatic activity.(69) However, the exact mechanism by which aspirin exerts its anticancer effects remains unclear. In a Swedish retrospective study, patients with chronic HBV or HCV infection who received low-dose aspirin (≤ 160 mg/day) had a significantly lower incidence of HCC. The protective effects of aspirin were duration dependent, and the 10-year liver-related mortality was also lower among aspirin users. In addition, this study indicated that long-term low-dose aspirin use was not associated with an increased risk of gastrointestinal bleeding.(68) In a randomized controlled trial comparing the incidence of adenoma in patients with a history of colorectal cancer, those who received 325 mg of aspirin daily had significantly fewer adenomas after a 12-month colonoscopy follow-up than the placebo group. The time to first adenoma detection was also longer in the aspirin group.(70)

In our study, statin use was associated with a lower risk of HCC in patients with HCV infections. Statins, HMG-CoA reductase inhibitors, inhibit cholesterol synthesis and are commonly used to reduce the incidence of cardiovascular disease.(71) In addition, statins also possess anti-inflammatory and anticancer properties. Their mechanisms of action include inducing cell apoptosis, inhibiting cell growth,

increasing radiosensitivity, and reducing invasion. Statins inhibit the mevalonate pathway, which is a crucial step in cholesterol synthesis, thereby interrupting cancer cell initiation, growth, and metastasis. (72–74) In their retrospective study, Tsan et al. found that statin use was associated with a lower risk of HCC, (75) consistent with the findings of the present study.

The present study revealed that antiviral therapy is associated with a higher risk of HCC in patients with HCV infection. This result may be related to Taiwan's national health insurance (NHI) payment policy. Before 2016, when direct-acting antivirals (DAAs) were first covered by Taiwan's NHI, most treatments for chronic HCV infection involved interferons, and NHI coverage was limited to patients with severe conditions. The coverage criteria included elevated liver enzyme levels and evidence of liver fibrosis. Patients who did not meet these criteria had to pay for out-of-pocket treatment, which many could not afford. (76) Our data revealed that male sex and older age are associated with a higher risk of HCC. In Taiwan, since the 1950s, most adult men have been required to serve the military for at least one to three years. Previously, public health knowledge and awareness regarding disease transmission were limited, leading to the common sharing of personal items, such as toothbrushes and razors in military group settings. This phenomenon contributes to the spread of viral hepatitis in men, resulting in a higher prevalence of the disease. (77)

The strengths of our study include its large sample size, long-term medical records from authoritative sources, and a large validation cohort. In addition to examining the association between HCQ use and HCC risk, we analyzed the effects of concurrent medications, comorbidities, sex, and age on HCC risk. However, our study had several limitations. First, although we assessed HCQ exposure based on prescription records, we were not able to analyze the severity of liver fibrosis or cirrhosis in the HCV-infected patients included in the study, as the Taiwan National Health Insurance Database does not contain this information. Second, it was impossible to verify whether patients took the medication as prescribed. Nevertheless, due to Taiwan's National Health Insurance system—where medication costs are low and patients are only eligible for the next month's prescription after using up the current supply—nearly all patients are presumed to have completed their medication before returning for a follow-up visit. Third, while the use of DAAs has led to significant progress in hepatitis C treatment in recent years, Taiwan's National Health Insurance only began to cover DAA antiviral drugs in 2017. The National Health Insurance database used for our study only included data up to 2016, so the impact of DAAs was not considered. Our study therefore lacked data on DAA use as a concurrent medication, and further investigation is needed to assess the efficacy of combining DAAs and HCQ in reducing HCC risk.

5 Conclusion

The use of HCQ may reduce the risk of HCC in patients with HCV infection, a topic rarely discussed in previous studies. Although some studies have explored the co-administration of sorafenib and HCQ to enhance anticancer effects (57, 58) our findings suggest that HCQ alone may serve as a preventive agent for HCC in patients with chronic HCV infection. However, the exact mechanism underlying the anti-cancer effects of HCQ remains unclear and requires further investigation.

Declarations

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Disclosure statement: The authors have no conflicts of interest to declare.

Data availability statement: The data used and analyzed in this study was obtained by Professor Chi-Ching Chang, our corresponding author, at his own expense from the Taiwan National Health Insurance Research Database. The data consists of deidentified data from the National Health Insurance population files from 2006 to 2018, and there are no concerns about privacy breaches.

Ethical approval information: This study was approved by the Institutional Review Board of Taipei Medical University (TMU JIRB-N201908055). This study complies with the requirements of the Declaration of Helsinki. According to the decision made by the Institutional Review Board of Taipei Medical University in 2019, informed consent is waived for this study.

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Authors' contributions:

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Drafting the article or revising it critically for important intellectual content: T.-M. Lin, C.-J. Chao, W.-Y. Kao, T.-T. Kuo, S.-C. Chen, J.-H. Chen, H.-Y. Lee, C.-C. Chang

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Table 3

Table 3 is available in the Supplementary Files section.

Figures

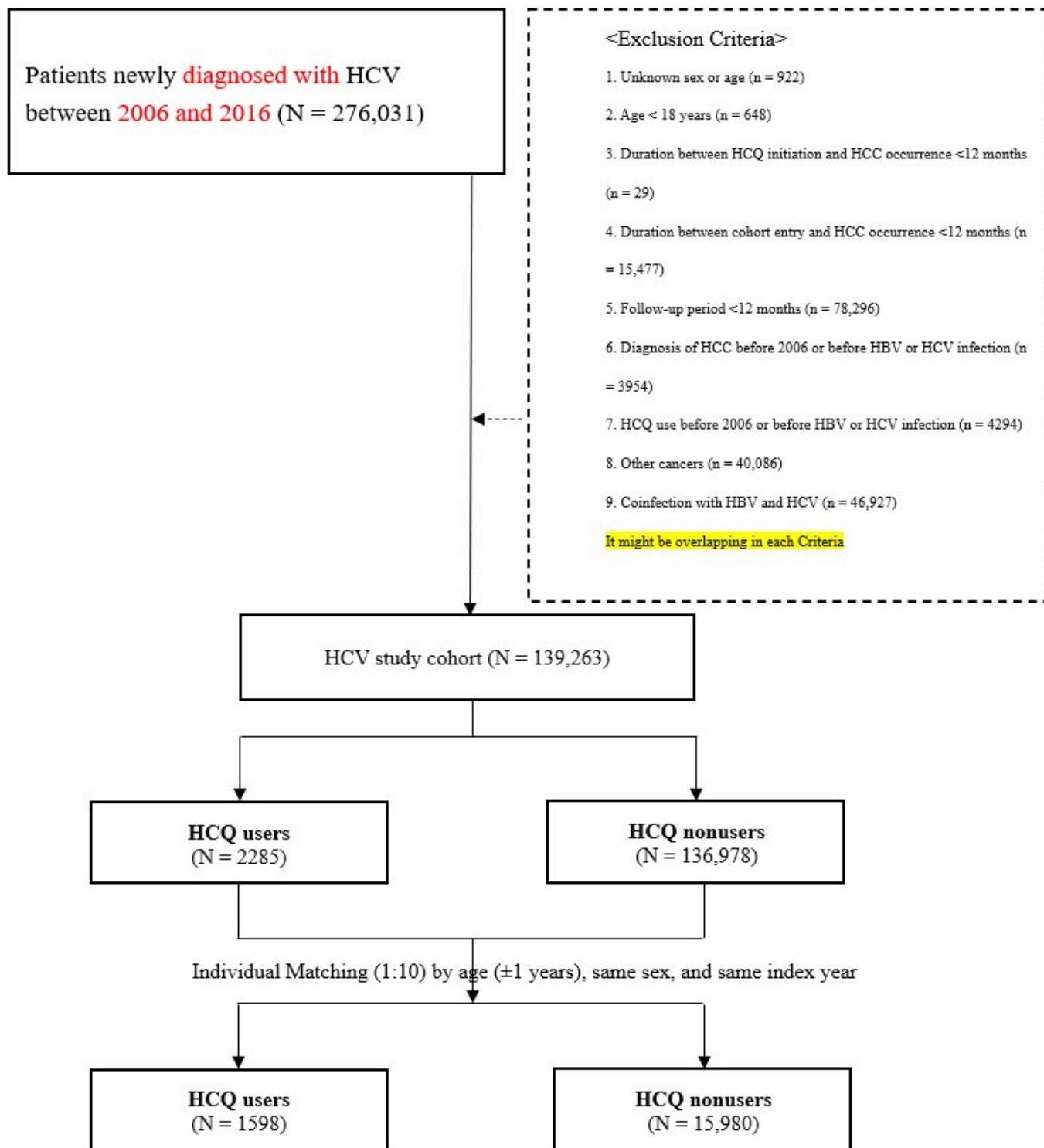


Figure 1

Flowchart of patient recruitment and data analysis

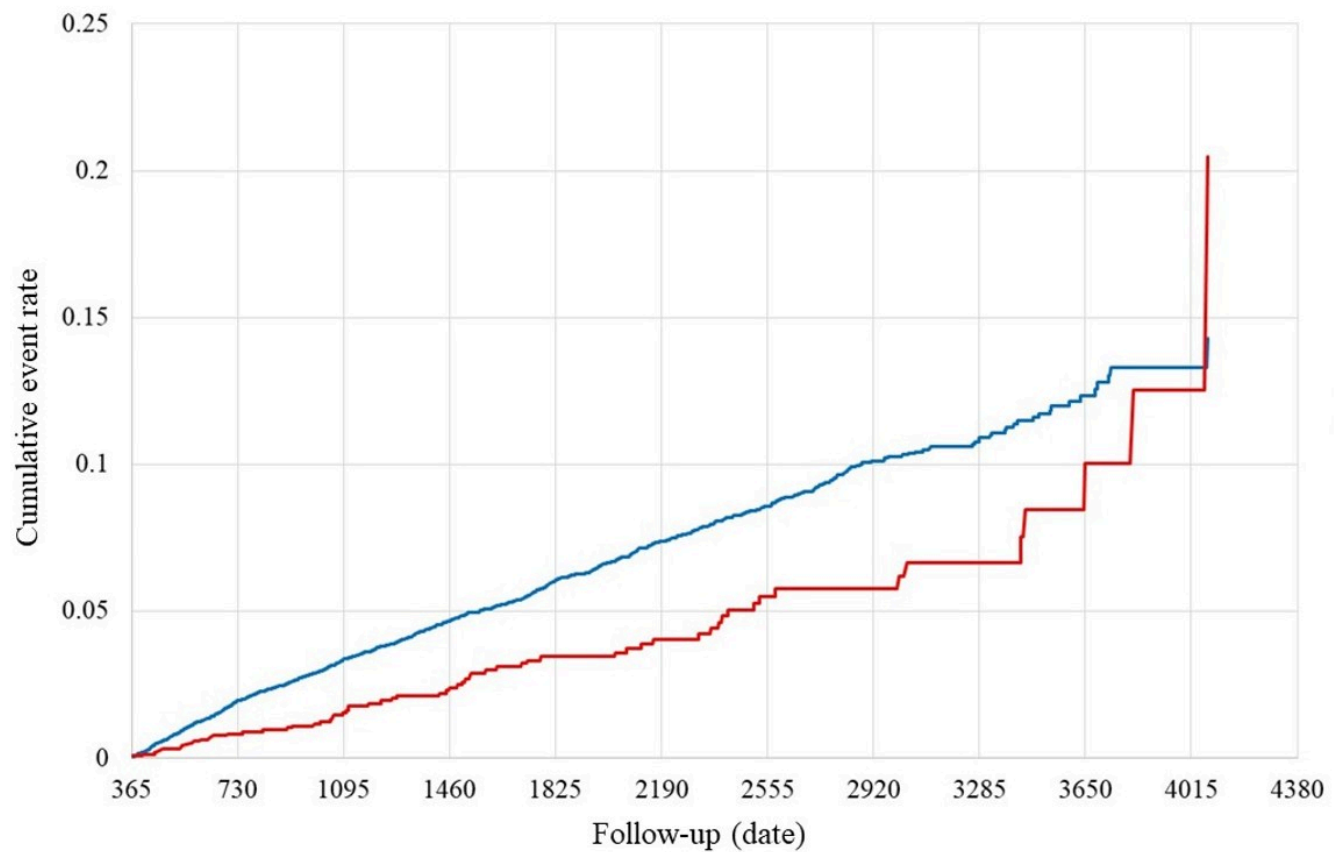


Figure 2

Comparison of the cumulative incidence of HCC between the HCQ users and non-users

Supplementary Files

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- [Table3.docx](#)