Association of Daily Aspirin Therapy With Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis C Virus Infection

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BACKGROUND & AIMS: **Aspirin therapy has been associated with reduced risk of colon cancer, but there is only limited evidence for its effects on risk of hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). We aimed to investigate the association of daily aspirin therapy with HCV-related HCC risk.**

METHODS: **In this cohort study, based on Taiwan's National Health Insurance Research Database, we screened 237,963 patients with chronic HCV infection for the period of 1997 through 2011. We excluded patients with confounding conditions and 2478 patients who continuously received daily aspirin therapy for 90 days or more (treated group) were randomly matched 1:2 with 4956 patients who had never received antiplatelet therapy (untreated group) by means of propensity scores. Cumulative incidence of, and hazard ratio (HR) for, HCC development were analyzed after we adjusted for patient mortality as a competing risk event.**

RESULTS: **The cumulative incidence of HCC in the treated group was significantly lower than that in the untreated group over 5 years (4.67%; 95% CI, 3.74%–5.59% vs 7.32%; 95% CI, 6.33%–8.30%; $P<.001$). In the multivariable regression analysis, aspirin therapy was independently associated with a reduced HCC risk (HR, 0.78, 95% CI, 0.64–0.95; $P = .011$), after adjustment for age per year, male sex, cirrhosis, liver decompensation, hyperlipidemia, statin use, and interferon therapy. Sensitivity subgroup analyses also verified this association (all HRs<1.0). In addition, older age (HR, 1.03 per year; 95% CI, 1.02–1.04), male sex (HR, 1.46; 95% CI, 1.21–1.77), and cirrhosis (HR, 3.13; 95% CI, 2.55–3.84) were independently associated with an increased HCC risk.**

CONCLUSIONS: **In a nationwide cohort study in Taiwan, we found aspirin therapy to be significantly associated with a reduced risk of HCV-related HCC.**

Keywords: Liver Cancer; Inflammation; Population; Asia.

Liver cancer is a common lethal malignancy worldwide and has risen from the third leading cancer to the second in terms of years of life lost between 2006 and 2016.[1] Discovering an effective way to prevent hepatocellular carcinoma (HCC) is therefore a critical public health issue. Hepatitis C virus (HCV) infection has been recognized as one of the most relevant risk factors of HCC.[2] Interferon therapy was the standard treatment for chronic HCV infection before the era of direct-acting antiviral (DAA); however, troublesome side effects and moderate virologic response rates limit its clinical use.[3] Fortunately, DAA has been successfully developed in recent years, allowing for HCV eradication to be achieved

Abbreviations used in this paper: **CI, confidence interval; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICD, International Classification of Diseases; NHIRD, National Health Insurance Research Database; NSAID, nonsteroidal anti-inflammatory drug; PUB, peptic ulcer bleeding; RCIPD, Registry for Catastrophic Illness Patient Database.**

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2020.04.036

in the majority of patients.[4] However, although antiviral therapy is associated with a decreased HCC risk, the risk is not completely eliminated.[5] In addition, barriers such as wealth disparity may limit the widespread use of antiviral therapy. Therefore, other effective methods in reducing HCC risk are expected.

Because of its anti-inflammatory properties, aspirin has been previously investigated for its possible chemopreventive effect in cancers that are related to chronic inflammation.[6] Aspirin therapy has been associated with a reduced cancer risk, particularly for colorectal cancer.[7] However, the effect of aspirin toward preventing other malignancies remains uncertain. Aspirin therapy has been reported to be associated with a reduced HCC risk in several large-scale studies[8–11]; however, information regarding HCV infection has been unclear, only partially disclosed, or limited in scale. For example, in the nested case control study within the Liver Cancer Pooling Project study,[9] only 52 cases with HCV infection were included. Recent studies have identified a relatively homogeneous cohort of patients experiencing chronic HBV infection that confirm the association of aspirin therapy with a reduced HCC risk.[12,13] However, a thorough clinical research of aspirin therapy on reducing HCV-related HCC risk remains lacking.

HCV-related HCC has been known to be a consequence of chronic inflammation, where antiplatelet therapy may diminish immune-mediated necroinflammation, liver fibrosis, and HCC development.[14] Therefore, aspirin therapy can potentially offer a means for preventing HCC. Importantly, previous experimental studies have shown that aspirin can inhibit the life cycle of HCV,[15,16] and that aspirin may inhibit HCC development through several molecular mechanisms.[17–19] Therefore, conducting a clinical study needs to be the next step toward examining the association of aspirin therapy with HCV-related HCC. We therefore designed a large-scale study to evaluate the association of daily aspirin therapy with the risk of HCV-related HCC.

What You Need to Know

Background

Aspirin therapy has been associated with reduced risk of colon cancer, but there is only limited evidence for its effects on risk of hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC).

Findings

In a nationwide cohort study in Taiwan, we found aspirin therapy to be significantly associated with a reduced risk of HCV-related HCC.

Implications for patient care

Patients with chronic HCV infection should receive aspirin therapy to reduce risk of HCC.

Methods

Study Design

In this cohort study, we retrieved data from Taiwan's National Health Insurance Research Database (NHIRD) for the period January 1, 1997 to December 31, 2011. The NHIRD contains claim data for more than 99% of the 23.38 million residents in Taiwan.[20] As outlined in our previous studies,[21–26] patients' demographic data, dates of clinic visits and hospitalization periods, disease diagnosis, therapeutic procedures, and details of prescriptions such as drug names, dates, duration, routes, dosages, and frequency can be identified (Supplementary Table 1). Diseases have been defined according to the International Classification of Diseases, 9th Revision (ICD-9) codes. The quality of this database in terms of both accuracy in medications and disease diagnosis has been well-validated in previous studies, for example, the use of aspirin for cardiovascular diseases.[27,28] The ICD codes used in this study are listed in Supplementary Table 2, and diseases must have been diagnosed at least 3 times in outpatient clinics or once during a hospitalization. The Research Ethics Committee of the National Health Research Institutes in Taiwan approved the present study.

Study Population

Figure 1 shows the patient selection process. We screened 237,963 patients with chronic HCV infection from the database. Patients with hepatitis B virus infection, other viral hepatitis, human immunodeficiency virus infection, and alcoholic liver disease were excluded. Because a refillable prescription with a total duration of 3 months is permitted for regular drug users in Taiwan, a selection criterion of 90 consecutive days was used for enrolling regular aspirin users. Irregular aspirin users, patients who received other antiplatelet therapies (eg, clopidogrel), and patients who received aspirin therapy before the initial diagnosis of HCV infection were also excluded. Patients who continued daily aspirin therapy for 90 days or more were identified as the aspirin-treated cohort, whereas patients who never received antiplatelet therapy throughout the whole database period were assigned to the untreated cohort. After matching the index dates of patients in the untreated cohort with those in the treated cohort, patients with a diagnosis of HCC and patients who received interferon-based therapy before the index dates were excluded in the 2 study cohorts. In total, 2478 patients who received

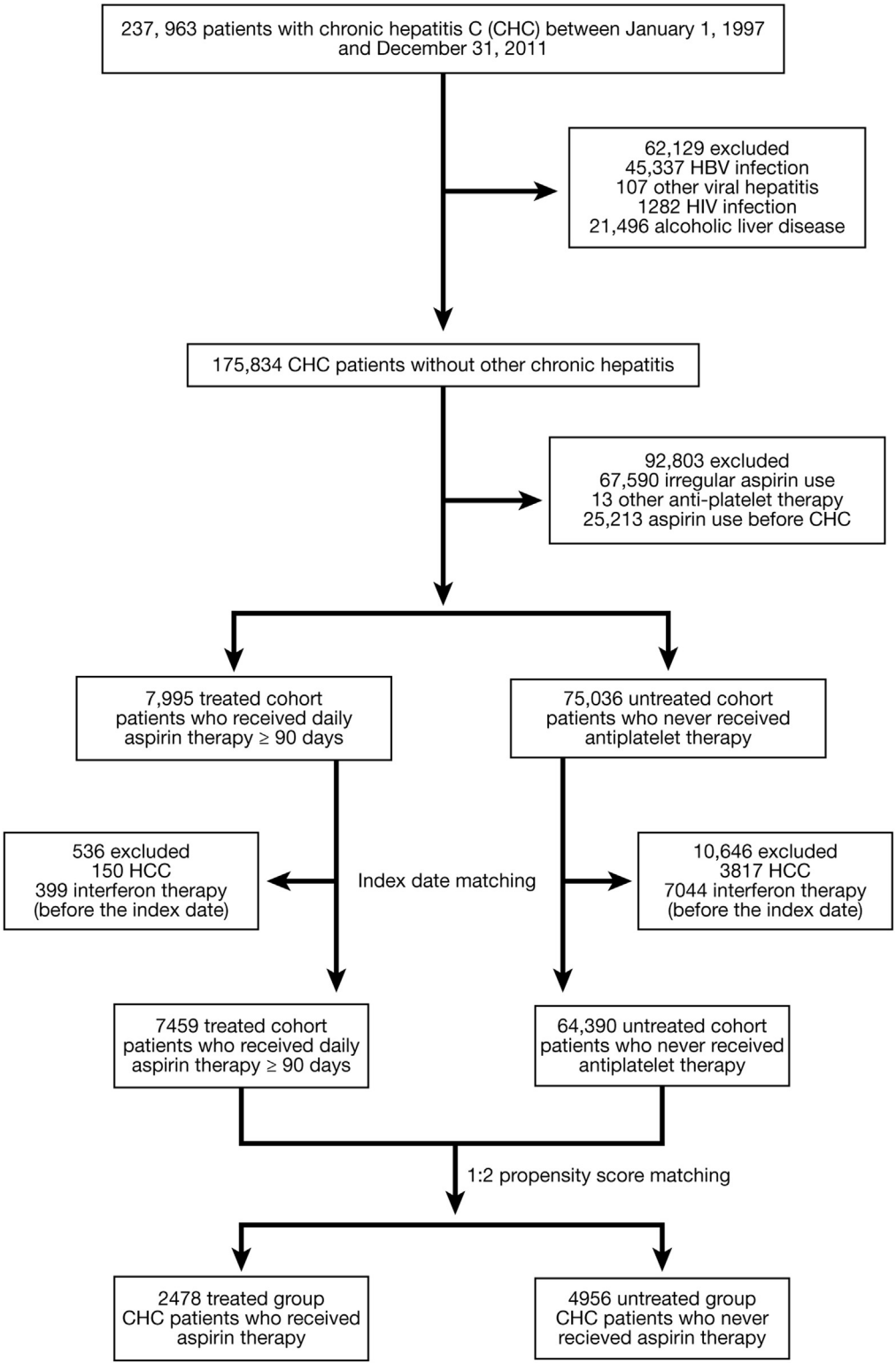

Figure 1. Selection of study participants. CHC, chronic hepatitis C; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus.

continuous aspirin therapy (treated group) were randomly matched 1:2 with 4956 patients who had never received antiplatelet therapy (untreated group) by means of propensity scores, which consisted of index date to the start of follow-up, baseline characteristics at the index date (age, sex, HCV follow-up duration, cirrhosis, liver decompensation, and cardiovascular-related diseases [ie, diabetes, hyperlipidemia, hypertension, coronary arterial disease, cerebral vascular disease, cardiac dysrhythmias, and peripheral vascular disease]), use of potentially chemopreventive medicines (ie, metformin, statins, and nonsteroidal anti-inflammatory drugs [NSAIDs]), along with interferon-based therapy.

Main Outcome Measurement

HCC occurrence was set as the major measured outcome. Patients in the treated group were followed up from the 180th day of initiating aspirin therapy (as the index date), with the patients who developed HCC before the index dates being excluded as part of the washout period. The index dates of the matched patients in the untreated group were defined as the same dates as those in the treated group and were matched by both age and sex. Study participants were followed up until the dates of HCC occurrence, death, or the end of the study period (December 31, 2011). The Registry for Catastrophic Illness Patient Database (RCIPD) is an official subsystem related to patients' reimbursement cost deduction, in which histopathologic confirmation or typical imaging characteristics are requested for the diagnosis of HCC.[23–26] The diagnosis of HCC was validated by registration in the RCIPD.

Risk Factor Assessment

In addition to age and sex, several major coexisting diseases that may be related to the risk of HCC development were evaluated at the index date of outcome follow-up, including cirrhosis, liver decompensation, diabetes, hyperlipidemia, and hypertension. Patients who regularly used the specific medications for diabetes, hypertension, or hyperlipidemia were also identified for the diagnosis of coexisting diseases. Liver cirrhosis with ascites, hepatic encephalopathy, or hepatorenal syndrome was defined as liver decompensation. In addition, metformin, statins, nonaspirin NSAIDs, and interferon-based therapy were considered to be medications with potentially chemopreventive effects, so their use was also analyzed. The users of metformin, statins, or nonaspirin NSAIDs were defined as those patients who took the medications for more than 1 day per week before the index dates of outcome follow-up. Interferon therapy should have been continuously used for at least 16 weeks during the follow-up period.

Statistical Analysis

Continuous variables and categorical variables of demographic data were compared by using the Student t test and the χ^2 test, respectively. By using a logistic regression model, propensity score analysis was performed to examine the comparability of the 2 study groups.[29] For assessing the balance of covariate distribution between the 2 study groups after propensity score matching, balance diagnostics was performed by means of standardized mean difference.[30] Cumulative incidence rates of HCC were calculated and compared by using a modified Gray method and the Kaplan-Meier method, respectively, with the differences in the full time-to-event distributions between the 2 study groups compared by a modified log-rank test.[23] To avoid risk overestimation, patient mortality/liver transplantation before HCC development was treated as a competing risk event. We further used univariable regression analysis to identify any potential risk factors for HCC development, with any independent risk factors being determined according to the results of multivariable regression analyses. Hazard ratios (HRs) were obtained in Cox proportional hazard models and then adjusted on the basis of the subdistribution of the competing risk.[31] In addition, we conducted a multivariable stratified analysis as a sensitivity analysis to evaluate the HRs of aspirin therapy in various patient subgroups. We managed the data through SAS, version 9.3 software (SAS Institute Inc, Cary, NC) and used the "cmprsk" package for R to construct the Cox proportional hazard models.[32]

Results

Study Participants

Table 1 shows the demographic characteristics of the 2 study groups. As shown in Supplementary Table 3, the covariates have been well-balanced between the 2 study groups after propensity score matching. Most patients started aspirin therapy during late middle age (median, 64.1 years), and of those in aspirin therapy, 1097 (44.3%), were male. The median duration of aspirin therapy was 4.0 years. Regarding the daily dosage of aspirin during therapy, 2461 of the patients (99.3%) took 100 mg or less. Clearly, low-dose aspirin was prescribed for the purpose of preventing cardiovascular diseases. After propensity score matching, HCV follow-up duration, cirrhosis, liver decompensation, cardiovascular-related diseases, and potentially chemopreventive drug use were found to not be significantly different between the 2 groups.

Cumulative Incidence of Hepatocellular Carcinoma

Figure 2 shows the cumulative incidences of HCC. After adjusting for the competing risk, the cumulative incidence of HCC in the aspirin-treated group was significantly lower than that in the untreated group over the span of 5 years (4.67%, 95% confidence interval [CI], 3.74%–5.59% vs 7.32%, 95% CI, 6.33%–8.30%; $P <$ .001). As shown in Supplementary Figure 1, we further demonstrate the cumulative incidences of HCC over 10 years. The 10-year cumulative incidences of HCC in the aspirin-treated group were significantly lower than those in the untreated group (11.23%, 95% CI, 9.31%–13.15% vs 14.89%, 95% CI, 12.32%–17.46%; $P <$ .001).

Table 1. Demographic Characteristics of the Study Participants[a]

Characteristics	Treated n = 2478	Untreated n = 4956	*P* value
Age, *y*			
Mean ± SD	63.2 ± 10.0	63.2 ± 10.0	.96
Median (IQR)	64.1 (55.8–70.8)	64.1 (55.8–70.8)	.94
Sex, n (%)			1.00
Male	1097 (44.3)	2194 (44.3)	
Female	1381 (55.7)	2762 (55.7)	
Daily aspirin dosage, *mg*		NA	
≤100	2461 (99.3)		
>100	17 (0.7)		
Aspirin therapy duration, *y*		NA	
Mean ± SD	4.6 ± 3.3		
Median (IQR)	4.0 (1.8–6.9)		
HCV follow-up duration,[b] *y*			
Mean ± SD	3.3 ± 2.4	3.3 ± 2.4	.82
Median (IQR)	2.7 (1.2–4.8)	2.7 (1.2–4.7)	.81
Liver cirrhosis	375 (15.1)	795 (16.0)	.33
Liver decompensation	54 (2.2)	110 (2.2)	.98
Cardiovascular-related diseases			
Diabetes	1070 (43.2)	2116 (42.7)	.71
Hyperlipidemia	772 (31.2)	1588 (32.0)	.45
Hypertension	1984 (80.1)	3915 (79.0)	.30
Coronary arterial disease	805 (32.5)	1507 (30.4)	.07
Cerebral vascular disease	509 (20.5)	981 (19.8)	.47
Cardiac dysrhythmias	187 (7.6)	380 (7.7)	.89
Peripheral vascular disease	26 (1.1)	52 (1.1)	1.00
Drug use			
Metformin	453 (18.3)	980 (19.8)	.13
Statin	114 (4.6)	226 (4.6)	.98
Nonaspirin NSAIDs	230 (9.3)	416 (8.4)	.22
Interferon therapy	95 (4.7)	215 (5.4)	.33
Propensity score			
Mean ± SD	0.3 ± 0.1	0.3 ± 0.1	.86
Median (IQR)	0.3 (0.2–0.4)	0.3 (0.2–0.4)	.85

HCV, hepatitis C virus; IQR, interquartile range; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation.
[a]Data are expressed as median (interquartile range) or number (percentage).
[b]HCV follow-up duration: duration from first date to diagnose chronic HCV infection to the index date.

Multivariable Analysis of Risk Factors

Table 2 reports the multivariable regression analysis. Aspirin therapy remained an independent factor that was associated with 22% risk reduction in HCC development (HR, 0.78; 95% CI, 0.64–0.95; $P = .011$), after adjustment for age per year, male sex, cirrhosis, liver decompensation, hyperlipidemia, statin use, and interferon therapy. In addition, an older age (HR, 1.03 per year; 95% CI, 1.02–1.04), male sex (HR, 1.46; 95% CI, 1.21–1.77), and cirrhosis (HR, 3.13; 95% CI, 2.54–3.84) were independently associated with an increased HCC risk.

Negative Control Study

The association between the use of another similar medication and HCC risk was evaluated. In the univariable regression analysis, beta blocker use (HR, 1.12;

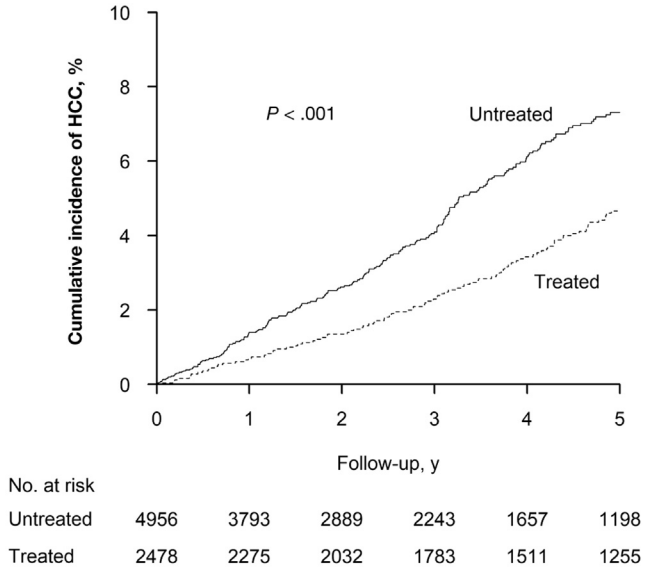

Figure 2. Cumulative incidence of hepatocellular carcinoma (HCC) development. Follow-up from 180 days after initiating aspirin therapy in the treated group.

95% CI, 0.87–1.44; $P = .394$) and acetaminophen use (HR, 1.30; 95% CI, 0.78–2.15; $P = .314$) were not associated with a decreased HCC risk.

Multivariable Stratified Analysis for Aspirin Therapy

Figure 3 presents the multivariable stratified analysis for each subgroup of patients. The association of aspirin therapy and a reduced HCC risk was verified in various patient subgroups, including those aged >65 years, female patients, those without underlying cirrhosis, those without coexisting hyperlipidemia, those with coexisting hypertension, non-metformin users, non-statin users, statin users, and non-interferon therapy receivers. Although a statistical significance was not reached in other patient subgroups, their HRs remained <1.0.

Sensitivity Study for a Longer Aspirin Therapy Period

For avoiding immortal time bias, we redefined the selection cutoff of aspirin use at 2 years, with patients then followed up from the second year of initiating aspirin therapy (as the index date). The median duration of aspirin therapy was 5.6 years. As shown in Supplementary Figure 2, the 10-year cumulative incidences of HCC in the aspirin-treated group were significantly lower than those in the untreated group (12.80%, 95% CI, 9.08%–16.53% vs 17.24%, 95% CI, 13.74%–20.75%; $P = .001$). In multivariable regression analysis, aspirin therapy was associated with reduced HCC risk (HR, 0.71; 95% CI, 0.55–0.93; $P = .012$). Furthermore, the cumulative days of aspirin use during the 2-year period before the index dates were calculated for investigating the effect of adherence to aspirin use. As shown in Supplementary Figure 3, the cumulative incidences of HCC in the ≥80% adherence group were not significantly lower than those in the <80% adherence group (10-year: 10.81%, 95% CI, 7.90%–13.72% vs 15.41%, 95% CI, 7.38%–23.43; $P = .967$).

Major Hemorrhage of Peptic Ulcer Disease

The cumulative incidence of peptic ulcer bleeding (PUB) during the follow-up period was evaluated, with PUB being defined as a major diagnosis of peptic ulcer disease that led to hospitalization and blood transfusion. As demonstrated in Supplementary Figure 4, the 10-year cumulative incidences of PUB in the aspirin-treated group were not significantly higher than those in the untreated group (4.85%, 95% CI, 3.58%–6.12% vs 3.71%, 95% CI, 2.73%–4.69; $P = .369$). However, as

Table 2. Cox Proportional Hazards Regression Model Analysis for Risk of Hepatocellular Carcinoma

		Univariable		Multivariable	
Variables	n	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treated vs untreated	2478	0.71 (0.59–0.87)	<.001	0.78 (0.64–0.95)	.011
Age per year	7434	1.05 (1.04–1.05)	<.001	1.03 (1.02–1.04)	<.001
Male	3291	1.38 (1.14–1.66)	<.001	1.46 (1.21–1.77)	<.001
Liver cirrhosis	1170	3.55 (2.93–4.31)	<.001	3.13 (2.54–3.84)	<.001
Liver decompensation	164	1.82 (1.09–3.05)	.022	0.72 (0.42–1.22)	.222
Diabetes mellitus	3186	1.12 (0.93–1.36)	.223		
Hyperlipidemia	2360	0.67 (0.53–0.85)	<.001	0.81 (0.64–1.03)	.088
Hypertension	5899	1.27 (0.99–1.62)	.055		
Metformin	1433	1.14 (0.90–1.46)	.279		
Statin	340	0.41 (0.18–0.92)	.031	0.57 (0.25–1.30)	.182
Nonaspirin NSAIDs	646	0.91 (0.67–1.24)	.550		
Interferon therapy	310	0.52 (0.34–0.80)	.003	0.75 (0.49–1.15)	.189

CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.

Characteristic	Event, No./Total No.		
Strata	Treated	Untreated	HR (95% CI)
Age group, y			
≤ 65	68/1323	84/2637	0.91 (0.66-1.25)
> 65	98/1155	186/2319	0.69 (0.54-0.88)
Sex			
Male	91/1097	132/2194	0.90 (0.69-1.18)
Female	75/1381	138/2762	0.66 (0.50-0.86)
Cirrhosis			
No	111/2103	154/4161	0.75 (0.59-0.96)
Yes	55/375	116/795	0.75 (0.55-1.03)
Diabetes			
No	98/1408	154/2840	0.77 (0.60-1.00)
Yes	68/1070	116/2116	0.77 (0.57-1.04)
Hyperlipidemia			
No	133/1706	215/3368	0.81 (0.65-1.00)
Yes	33/772	55/1588	0.67 (0.43-1.03)
Hypertension			
No	29/494	49/1041	0.80 (0.50-1.28)
Yes	137/1984	221/3915	0.76 (0.61-0.93)
Metformin			
No	138/2025	219/3976	0.78 (0.63-0.96)
Yes	28/453	51/980	0.76 (0.47-1.21)
Statin			
No	165/2364	265/4730	0.79 (0.65-0.96)
Yes	1/114	5/226	0.17 (0.03-0.97)
Nonaspirin NSAIDs			
No	146/2248	247/4540	0.75 (0.61-0.93)
Yes	20/230	23/416	0.94 (0.53-1.67)
Interferon therapy			
No	158/2277	256/4591	0.79 (0.65-0.96)
Yes	8/201	14/365	0.50 (0.18-1.43)
Overall	166/2478	270/4956	0.78 (0.64-0.94)

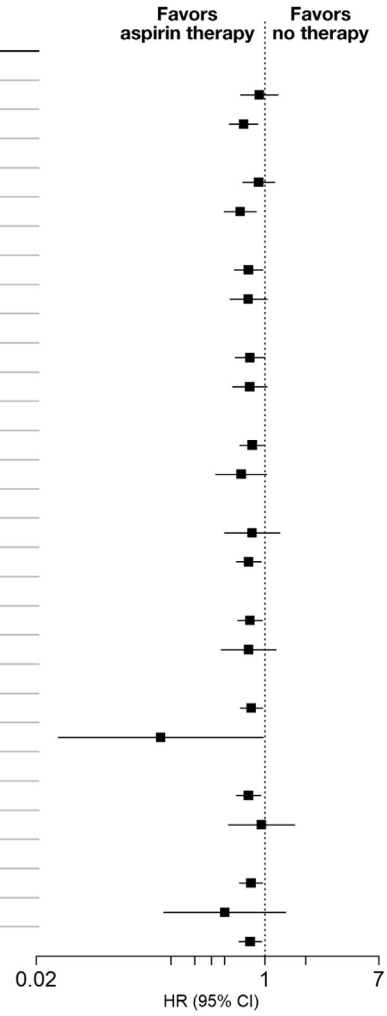

Figure 3. Multivariable stratified analyses of association between aspirin therapy and hepatocellular carcinoma development. CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

shown in Supplementary Figure 5, the PUB risk in the cirrhotic aspirin users was significantly higher compared with the risk in the non-cirrhotic users over 10 years (8.57%, 95% CI, 4.36%-12.77% vs 4.17%, 95% CI, 2.88%–5.46%; $P = .007$). Even so, only 20 and 58 PUB events were detected in the 385 cirrhotic aspirin users and the 2093 non-cirrhotic users, respectively.

Discussion

In the present study, we first report that daily low-dose aspirin therapy is significantly associated with a reduced risk of HCC in patients with chronic HCV infection. Although antiviral therapy is certainly the mainstay toward reducing HCC risk in patients with chronic HCV infection, this type of therapy, such as DAA, may be inaccessible to every patient. However, the prevention of HCC remains urgent for millions of HCV carriers in the world.[33] In addition, although patients receive antiviral therapy, HCC risk is not totally eliminated.[5,34,35] Aspirin is an inexpensive medicine and has been well-studied for its chemopreventive effects in colorectal cancer[12,13]; however, the available clinical data on HCC prevention, particularly in HCV-related HCC, remain needed. Our findings may be of help in future efforts toward further improving the chemoprevention of HCV-related HCC, which may be beneficial to patients worldwide.

The experimental findings also defend the conclusion of this study. Not only does aspirin provide an anti-inflammatory effect via blocking thromboxane A2 and cyclooxygenase, it may also inhibit immune-mediated hepatocarcinogenesis.[14] Specifically, aspirin can inhibit HCV entry by down-regulating claudin-1,[16] with the expression of HCV RNA and related protein also reduced.[15] Using a rat-based model for the study of cirrhosis, aspirin showed a beneficial effect on stopping fibrosis progression and improving liver regeneration.[36] Therefore, aspirin therapy may be an excellent adjuvant treatment in patients with chronic HCV infection. Moreover, several possible molecular mechanisms regarding the antioncogenic effect of aspirin therapy have been identified. For example, abnormal lipid metabolism is a hallmark of carcinogenesis in HCC cells, and aspirin has the ability to suppress the alterations of metabolism by disrupting the nuclear factor kappa B signaling.[18] In addition, aspirin can induce beclin-1–dependent autophagy and trigger human HCC cell

death.[17] Aspirin can also induce HCC cell apoptosis through a caspase-independent mechanism, whereas a synergistic effect of aspirin and sorafenib was observed in a xenograft mice model.[19] Current experimental data suggest that using aspirin to reduce HCC risk is not an unreasonable form of therapy.

The risk of aspirin-induced major hemorrhage has been both a concern and well-studied in long-term users,[37] with the benefits and harms of aspirin therapy needing to be carefully balanced, as recommended in the practice guidelines.[38] In this cohort study conducted for the purpose of analyzing the effects of regular aspirin use, patients who were able to tolerate aspirin therapy for at least 90 days were selected, where the risk of major peptic ulcer hemorrhage was not significantly increased in aspirin users, compared with that of aspirin non-users. However, risk underestimation remains possible because of the patient selection criteria; therefore, care should still be taken during the course of aspirin therapy. It is worth noting that aspirin therapy may be associated with an increased risk of major bleeding in cirrhotic patients, when compared with that of non-cirrhotic patients. Cirrhosis is a well-known risk factor for peptic ulcer hemorrhage. With a tendency toward bleeding in cirrhotic patients, a bleeding complication may be more likely to happen than usual.[39] Unless the need for aspirin is strongly indicated, aspirin therapy should be suggested with caution in mind.

Several limitations should also be mentioned with regard to this study. First, this was a retrospective cohort design. Although we matched all the potential confounders between the 2 study groups, a selection or observational bias is possible. However, on the basis of a large-scale and well-validated database, this study may overcome any possible bias to illuminate a clinically important association. Second was the use of over-the-counter aspirin. Because aspirin is fully reimbursed by the NHI in Taiwan, a regular aspirin user would not take aspirin out of pocket. Importantly, even though some patients in the untreated group might have used over-the-counter aspirin, the difference in HCC risk between the treated and the untreated groups could thus be underestimated. The conclusion of this study remains unchanged. Third, some aspirin users might have discontinued aspirin during the follow-up period. In this quasi-experimental study design mimicking the intent-to-treat analysis, although patients who received a short duration of aspirin therapy might be included, the association of aspirin therapy with the HCC risk was therefore conservatively evaluated. The conclusion of this study should be unchanged. Fourth, most patients were in the late to middle age category, and the ideal age at aspirin initiation is unknown. However, it is better for aspirin therapy to be initiated before the development of cirrhosis. Fifth, DAA therapy for hepatitis C had not been developed during the study period. Although both interferon and DAA can reduce HCC risk,[5,34,35] the findings regarding interferon therapy in this study may not be directly inferred to DAA therapy. Sixth, although the NHIRD data after 2011 can be updated, our analysis is limited by the previously applied database version. However, in this large-scale, long-term cohort study, we are confident to conclude the findings of our study.

In summary, the results of this large-scale, long-term cohort study suggest that daily low-dose aspirin therapy is significantly associated with a reduced risk of HCC development in patients with chronic HCV infection.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.04.036.

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Yao-Chun Hsu (Conceptualization: Lead; Data curation: Equal; Formal analysis: Lead; Validation: Equal; Writing – original draft: Lead)

Hsiao-Ching Tseng (Conceptualization: Supporting; Data curation: Supporting; Formal analysis: Supporting; Investigation: Lead; Methodology: Lead; Software: Lead)

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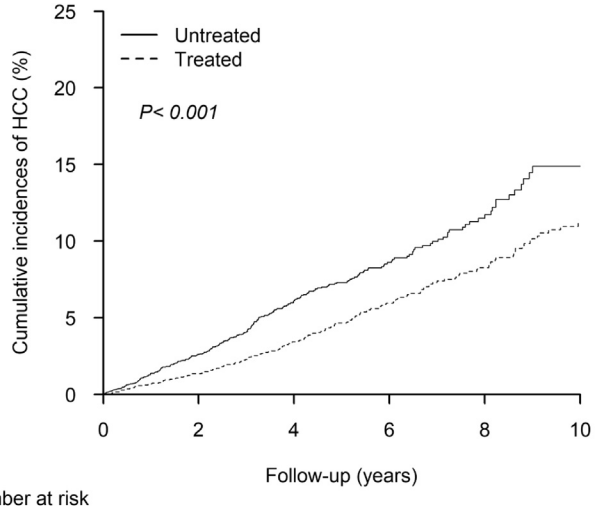
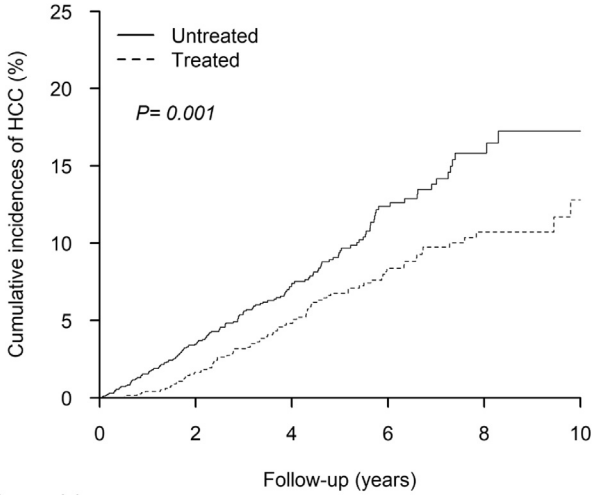
Conflicts of interest
The authors disclose no conflicts.

Funding
Supported in part by the Ministry of Science and Technology (107-2314-B-075A-002), National Yang-Ming University (107F-M01), the Ministry of Health and Welfare (MOHW108-TDU-B-211-124019), Taipei Veterans General Hospital (V108E-004-1 and 107VACS-003), and Taichung Veterans General Hospital (108DHA0500066), Taiwan.



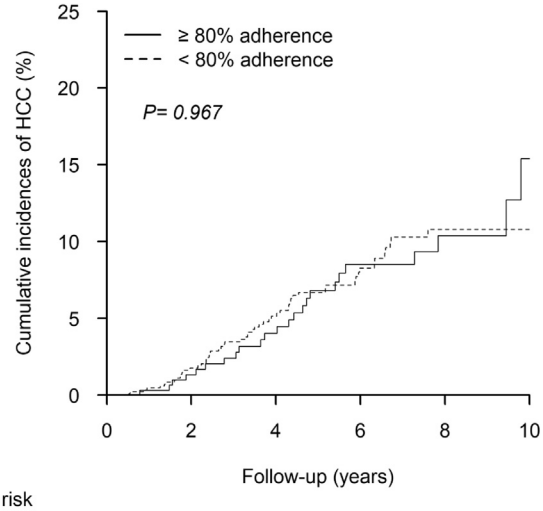
Number at risk						
Untreated	4956	2889	1657	792	288	74
Treated	2478	2032	1511	1003	528	204

Supplementary Figure 1. Cumulative incidence of hepatocellular carcinoma (HCC) development over 10 years. Follow-up from 180 days after initiating aspirin therapy in the treated group.



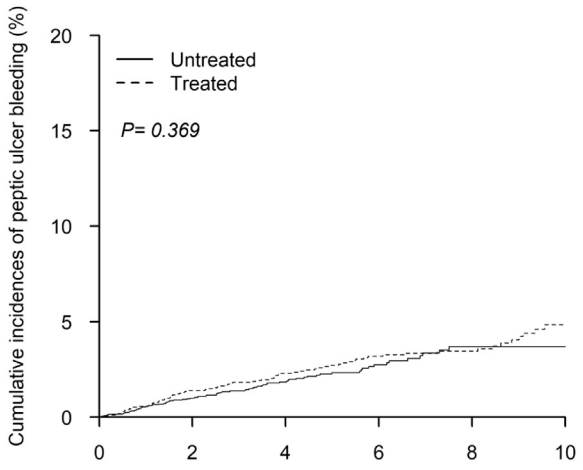
Number at risk						
Untreated	2372	1472	745	309	99	12
Treated	1186	966	662	378	168	44

Supplementary Figure 2. Cumulative incidence of hepatocellular carcinoma (HCC) development in the aspirin-treated ($\geq$2 years) or untreated groups. Follow-up from 2 years after initiating aspirin therapy in the treated group.



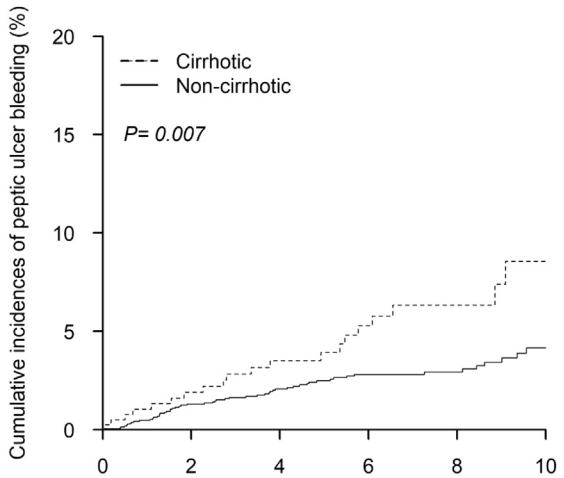
Number at risk						
≥ 80% adherence	316	272	196	117	60	17
< 80% adherence	870	694	466	261	108	27

Supplementary Figure 3. Cumulative incidence of hepatocellular carcinoma (HCC) development in the $\geq$80% adherence or $<$80% adherence groups in patients who received aspirin therapy $\geq$2 years. Follow-up from 2 years after initiating aspirin therapy in the treated group.



Number at risk						
Untreated	4955	2920	1718	818	301	76
Treated	2478	2035	1526	1010	533	208

Supplementary Figure 4. Cumulative incidence of peptic ulcer bleeding in the aspirin-treated or untreated groups.



Number at risk						
Cirrhotic	385	276	187	103	47	19
Non-cirrhotic	2093	1759	1339	907	486	189

Supplementary Figure 5. Cumulative incidence of peptic ulcer bleeding among cirrhotic or non-cirrhotic patients in the aspirin-treated group.

Supplementary Table 1. The Used Drug Codes of Aspirin Therapy in This Study

ATC code	Taiwan NHI code	Drug name	Ingredient	Dosage (mg)	Form
N02BA01	A003092100	Aspirin tablets 500 mg "S.Y."	Aspirin	500	Tablet
B01AC06	A004813100	Aspirin tablets "VPP"	Aspirin	324	Tablet
B01AC06	A021870100	Astar tablets (aspirin) "S.Y."	Aspirin	162	Tablet
B01AC06	A023534100	Ropal tablets (aspirin) "ROYAL"	Aspirin	100	Tablet
B01AC06	A024465100	Aspirin tablets "JOHNSON"	Aspirin	100	Capsule
N02BA01	A025160100	Aspirin F.C. tablets 500 mg "TAI YU"	Aspirin	500	Capsule
N02BA51	A026164100	Aspirin caffeine tablets "LITA"	Aspirin Caffeine	350 30	Tablet
N02BE51	A029740100	A.A.C. tablets	Acetaminophen (=Paracetamol) Aspirin Caffeine anhydrous	250 250 65	Tablet
N02BA01	A032045100	Aspirin E.F.C. tablets 650 mg "KOJAR"	Aspirin	650	Tablet
B01AC06	A036599100	Cadiopirin tablets (aspirin) 100 mg "VPP"	Aspirin	100	Tablet
B01AC06	A040658100	Asrin E.C. tablets 165 mg "H.S."	Aspirin	165	Tablet
N02BA01	A040826100	Subilin enteric-coated capsules 500 mg "H.S."(aspirin)	Aspirin	500	Capsule
B01AC06	A041018100	Nimape enteric F.C. tab. 100 mg	Aspirin	100	Tablet
B01AC06	A0429341G0	Sulin enteric-microencapsulated capsules 100 mg "WINSTON" (aspirin)	Aspirin	100	Capsule
B01AC06	A044016100	Sinlo enteric-microencapsulated capsules 100 mg "H.S" (aspirin)	Aspirin	100	Capsule
B01AC06	A0440161G0	Sinlo enteric-microencapsulated capsules 100 mg "H.S" (aspirin)	Aspirin	100	Capsule
B01AC06	A044069100	Acetyl salicylic acid tablets "T.L.B"	Aspirin	324	Tablet
B01AC06	A044578100	Synlet enteric-microencapsulated capsules 100 mg	Aspirin	100	Capsule
B01AC06	A048339100	Sintan enteric coated tablets 100 mg "MEIDER"	Aspirin	100	Tablet
N02BA01	A0483391G0	Sintan enteric coated tablets 100 mg "MEIDER"	Aspirin	100	Tablet
B01AC06	A0485421G0	Encinlo E.M. capsules 100 mg "UELIAN"	Aspirin	100	Capsule
B01AC06	A054863100	Lopirin enteric-coated tablets 81 mg	Aspirin	81	Tablet
M03BC51	AC29754100	Musolin tablets "S.D."	Orphenadrine citrate Aspirin Caffeine anhydrous	25 385 30	Tablet
B01AC06	AC37344100	Bokey enteric-microencapsulated capsules 100 mg (aspirin)	Aspirin	100	Capsule
B01AC06	AC373441G0	Bokey enteric-microencapsulated capsules 100 mg (aspirin)	Aspirin	100	Capsule
B01AC06	AC37702100	Kersan tablets 100 mg (aspirin) "CHINTENG"	Aspirin	100	Tablet
B01AC06	AC41220100	Asplatelet E.C. capsule 100 mg "PBF" (aspirin)	Aspirin	100	Capsule

Supplementary Table 1. Continued

ATC code	Taiwan NHI code	Drug name	Ingredient	Dosage (mg)	Form
B01AC06	AC41511100	Encine E.M. capsules 100 mg "EVEREST"	Aspirin	100	Capsule
B01AC06	AC415111G0	Encine E.M. capsules 100 mg "EVEREST"	Aspirin crystal enteric coated	100	Capsule
B01AC06	AC41814100	Aspicore enteric-microencapsulated cap. 100 mg (aspirin) "WEIDAR"	Aspirin	100	Capsule
B01AC06	AC418141G0	Aspicore enteric-microencapsulated cap. 100 mg (aspirin) "WEIDAR"	Aspirin	100	Capsule
B01AC06	AC42461100	Fusen enteric microencapsulated capsules 100 mg "CHINTENG"	Aspirin	100	Capsule
B01AC06	AC424611G0	Fusen enteric microencapsulated capsules 100 mg "CHINTENG"	Aspirin	100	Capsule
B01AC06	AC42774100	Ansin E.C. tablets 100 mg "EVEREST" (aspirin)	Aspirin	100	Tablet
B01AC06	AC42934100	"Sulin enteric-microencapsulated capsules 100 mg ""WINSTON" "(aspirin)"	Aspirin	100	Capsule
B01AC06	AC43139100	Clotstop tablets 100 mg "Y.Y."	Aspirin	100	Tablet
B01AC06	AC43142100	Fosen EFC tablets 100 mg "CHINTENG"	Aspirin	100	Tablet
B01AC06	AC43212100	Julrin enteric-coated tablets	Aspirin	100	Tablet
B01AC06	AC43254100	Antache enteric coated tablets 100 mg	Aspirin	100	Tablet
B01AC06	AC43309100	Aspa E. M.C. 100 mg "YU SHENG" (aspirin)	Aspirin	100	Capsule
B01AC06	AC433091G0	Aspa E. M.C. 100 mg "YU SHENG" (aspirin)	Aspirin	100	Capsule
B01AC06	AC43663100	Ascotyl enteric-microencapsulated capsules 100 mg "STANDARD"	Aspirin	100	Capsule
B01AC06	AC436631G0	AScotyl enteric-microencapsulated capsules 100 mg "STANDARD"	Aspirin	100	Capsule
B01AC06	AC43664100	Espin E. M. capsules 100 mg (aspirin)	Aspirin	100	Capsule
B01AC06	AC436641G0	Espin E. M. capsules 100 mg "EVEREST" (aspirin)	Aspirin	100	Capsule
B01AC06	AC44176100	Thromkey enteric-microencapsulated capsules 100 mg (aspirin) "SWISS"	Aspirin	100	Capsule
B01AC06	AC441761G0	Thromkey enteric-microencapsulated capsules 100 mg (aspirin) "SWISS"	Aspirin	100	Capsule
B01AC06	AC48542100	Encinlo E.M. capsules 100 mg "UELIAN"	Aspirin	100	Capsule
B01AC06	AC495361G0	Cardiopirin enteric coated tablets 100 mg (aspirin)	Aspirin	100	Tablet
B01AC06	AC548631G0	Lopirin enteric-coated tablets 81 mg	Aspirin	81	Tablet
B01AC06	AC54985100	Aspire enteric-microencapsulated capsules 100 mg	Aspirin	100	Capsule

Supplementary Table 1. Continued

ATC code	Taiwan NHI code	Drug name	Ingredient	Dosage (mg)	Form
B01AC06	AC549851G0	Aspire enteric-microencapsulated capsules 100 mg	Aspirin	100	Capsule
B01AC06	AC551041G0	Un-impede E.F.C. tablets 81 mg“MACRO”	Aspirin	81	Tablet
B01AC06	BC24025100	Aspirin protect 100	Aspirin	100	Tablet
B01AC06	BC240251G0	Aspirin protect 100	Aspirin	100	Tablet
B01AC06	N011693100	Aspirin tablets "SHIN LON"	Aspirin	300	Tablet

Supplementary Table 2. The ICD Codes Used in This Study

		ICD-9 code
1	Chronic hepatitis C	07041, 07044, 07051, 07054, V0262, 070.7
2	Chronic hepatitis B	070.2, 070.3, V02.61
3	Other viral hepatitis	573.2, 573.1
4	Human immunodeficiency virus disease	042
5	Alcoholic liver disease	571.0, 571.2, 571.3
6	Cirrhosis	571.5, 571.6
7	Liver decompensation	789.5, 572.2, 572.4
8	Diabetes mellitus	250, 648.0
9	Hyperlipidemia	272.0–272.4
10	Hypertension	401–405
11	Coronary arterial disease	410–414
12	Cerebral vascular disease	430–438
13	Cardiac dysrhythmias	427
14	Peripheral vascular disease	443
15	Hepatocellular carcinoma	155.0
16	Peptic ulcer bleeding	531.0, 531.1, 531.2, 531.4, 531.5, 531.6, 532.0, 532.1, 532.2, 532.4, 532.5, 532.6, 533.0, 533.1, 533.2, 533.4, 533.5, 533.6, 534.0, 534.1, 534.2, 534.4, 534.5, 534.6

ICD, International Classification of Diseases.

Supplementary Table 3. Balance Diagnostics for Assessing the Balance of Covariate Distribution Between the Two Study Groups After Propensity Score Matching

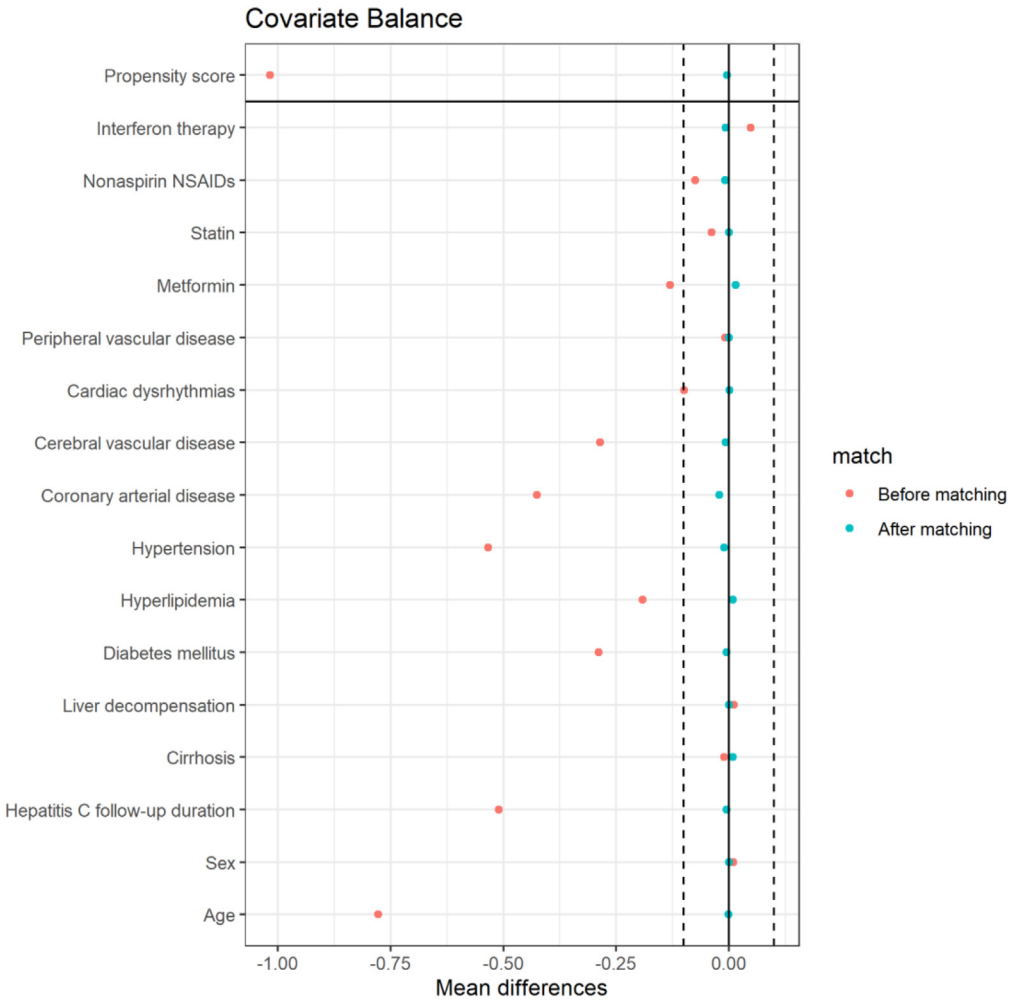
Balance measures: standardized mean difference (threshold < 0.1)

	Type	Diff. adjustment	M. threshold
Age	Contin.	-0.0012	Balanced, <0.1
Sex	Binary	0.0000	Balanced, <0.1
Hepatitis C follow-up duration	Contin.	-0.0055	Balanced, <0.1
Cirrhosis	Binary	0.0091	Balanced, <0.1
Liver decompensation	Binary	0.0004	Balanced, <0.1
Diabetes mellitus	Binary	-0.0048	Balanced, <0.1
Hyperlipidemia	Binary	0.0089	Balanced, <0.1
Hypertension	Binary	-0.0107	Balanced, <0.1
Coronary arterial disease	Binary	-0.0208	Balanced, <0.1
Cerebral vascular disease	Binary	-0.0075	Balanced, <0.1
Cardiac dysrhythmias	Binary	0.0012	Balanced, <0.1
Peripheral vascular disease	Binary	0.0000	Balanced, <0.1
Metformin	Binary	0.0149	Balanced, <0.1
Statin	Binary	-0.0004	Balanced, <0.1
Nonaspirin NSAIDs	Binary	-0.0089	Balanced, <0.1
Interferon therapy	Binary	-0.0075	Balanced, <0.1
Propensity score	Contin.	-0.0044	Balanced, <0.1

Contin., Continuous; Diff., Difference.

Balance tally for mean differences

	Count
Balanced, <0.1	17
Not balanced, >0.1	0


Covariate Balance
Propensity score
Interferon therapy
Nonaspirin NSAIDs
Statin
Metformin
Peripheral vascular disease
Cardiac dysrhythmias
Cerebral vascular disease
Coronary arterial disease
Hypertension
Hyperlipidemia
Diabetes mellitus
Liver decompensation
Cirrhosis
Hepatitis C follow-up duration
Sex
Age
-1.00
-0.75
-0.50
-0.25
0.00
Mean differences
match
Before matching
After matching