Relation Between Hepatitis C Virus Exposure and Risk of Osteoporosis

A Nationwide Population-based Study

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Abstract: The effect of hepatitis C virus (HCV) exposure on bone mineral density without advanced liver disease remains debated. Thus, we assessed the relation between HCV exposure and the risk of osteoporosis.

From 2000 to 2011, patients aged >20 years with HCV exposure were identified from the Longitudinal Health Insurance Database 2000. Of the 51,535 sampled patients, 41,228 and 10,307 patients were categorized as the comparison and the HCV exposure cohorts, respectively.

The overall incidence of osteoporosis in the HCV exposure cohort was higher than in the comparison cohort (8.27 vs 6.19 per 1000 person-years; crude hazard ratio = 1.33, 95% confidence interval = 1.20–1.47). The incidence of osteoporosis, higher in women than in men, increased with age and comorbidity of hypertension, hyperlipidemia, and heart failure. The risk of developing osteoporosis was significantly higher in the HCV exposure cohort than in the comparison cohort after adjusting for age, sex, diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis. However, the risk of osteoporosis contributed by HCV decreased with age and the presence of comorbidity. Furthermore, the risk of osteoporotic fracture did not differ significantly between patients exposed to HCV and the comparison cohorts.

HCV increases the risk of osteoporosis, but no detrimental effect on osteoporotic fracture was observed in this study. Furthermore, HCV may be less influential than other risk factors, such as hypertension, hyperlipidemia, and heart failure, in contributing to the development of osteoporosis.

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INTRODUCTION

A negative balance between the formation and resorption of bone mass can lead to the development of osteoporosis. Moreover, osteoporosis characterized by skeletal fragility resulting from reduced bone mass and disrupted bone micro-architecture. Osteoporosis increases the risk of fracture and thus has been considered a major public health concern. Traditionally, the development of osteoporosis is related to several risk factors, such as aging, immobility, hypertension, antihypertensive agents, hyperparathyroidism, menopause, diabetes mellitus, corticosteroid usage, low calcium intake, vitamin D deficiency, and genetic vulnerability.

Osteoporotic fractures mainly consist of vertebral fracture and hip fracture. Vertebral fracture is the most common osteoporotic fracture, but only from one-third to one quarter of the patients with vertebral fracture can be clinically identified. Furthermore, it is reported that asymptomatic vertebral fractures are associated with future hip fracture by threefold and other nonvertebral fracture by twofold. Hip fracture is the second common osteoporotic fracture and it may incur substantial healthcare costs resulted from disability. Furthermore, the effect of hip fracture on mortality increase can adversely extend up to 10 years or more. The mortality following a hip fracture generally increases with the increment of age and is greater in men, but the sex difference declines after age 80. Although the rates of hip fracture have declined in the West, the rate is increasing in the developing world. It is estimated that 50% of hip fractures worldwide will occur in Asia by 2050. The functional outcome and increased mortality of osteoporotic fracture are heterogeneous and depend on age, activity of daily living prior to fracture, pre-fracture comorbidities, and the cognition.

Hepatitis C virus infection (HCV) is a global health problem estimated to affect 170 million people worldwide. Hepatitis C virus infection is a hepatotropic virus that mainly...
causes inflammation and fibrosis of the liver. It is reported that ~20% of HCV-infected patients will progress to liver cirrhosis. The late hepatic sequelae include chronic hepatitis, cirrhosis, and even hepatocellular carcinoma. However, HCV can also cause several extrahepatic manifestations, such as diabetes mellitus, rheumatic disorders, lymphoproliferative disease, cardiovascular events, and cognitive impairment. Although the role of osteoporosis as a sequence of cirrhosis or advanced liver disease has been thoroughly documented, the effect of HCV exposure on bone mineral density in the absence of advanced liver disease remains debated. Some scholars have proposed that chronic HCV infection without liver cirrhosis contributes to reduced bone mineral density, whereas other scholars have asserted the opposite.

To assess the association between HCV exposure and subsequent development of osteoporosis, we conducted a nationwide population-based cohort study by analyzing data from a nationwide medical database, the National Health Insurance Research Database (NHIRD).

METHODS

Data Source
The National Health Insurance (NHI) program, initiated on March 1, 1995, provides comprehensive coverage for the medical care of Taiwan residents. At the end of 2014, 23.75 million people (~99.9% of the population) were enrolled in the program. In cooperation with the Bureau of National Health Insurance (BNHI), the National Health Research Institutes established several data sets for public use, including the Longitudinal Health Insurance Database 2000 (LHID2000), a cohort data set comprising 1,000,000 randomly selected cases from the registry of NHI beneficiaries in 2000. To maintain confidentiality, personal information, such as patient identification numbers and sensitive personal data, are encrypted in the database, and International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes are used for disease classification. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Participants
From 2000 to 2011, patients aged 20 years and older with diagnosed HCV infection (ICD-9-CM codes 070.41, 070.44, 070.51, and 070.54) identified from the LHID2000 comprised the HCV infection cohort. The date for HCV exposure coding was designated as the index date. Patients with a history of osteoporosis (ICD-9-CM codes 733.0 and 733.1) and hepatitis B virus (HBV) infection (ICD-9-CM codes 070.20, 070.22, 070.30, and 070.32) diagnosed before the index date, those with missing information, and those younger than 20 years were excluded. Using 1:4 case-control studies is to increase the power and to control possible confounding. Based on the statistical efficiency does not gain much when m > 4, we constructed a 1:4 matched cohort study. For each HCV case, 4 insurers with no history of HCV exposure, HBV infection, and osteoporosis were assigned to a comparison cohort and frequency matched with the HCV exposure cohorts according to age (every 5-year span), sex, and index year. Individuals were excluded from the comparison cohort using the same criteria used for the HCV exposure cohort.

Outcome and Comorbidities
The primary endpoint in this study was defined as the diagnosis of osteoporosis. Each participant was followed from the index date until the endpoint, withdrawal from the NHI program, or December 31, 2011. The baseline characteristics of participant comorbidities were also analyzed; the comorbidities included diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), heart failure (ICD-9-CM code 428), stroke (ICD-9-CM codes 430–438), obesity (ICD-9-CM code 278), and cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6).

Statistical Analyses
The chi-square test and t test for categorical and continuous variables, respectively, were first used to compare the distributions of age, sex, and baseline comorbidities between the HCV exposure and the comparison cohorts. The incidence densities of osteoporosis were estimated in person-years for the various risk factors. To estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of osteoporosis, the univariate and multivariate Cox proportional hazards regression model was used. Multivariable models were simultaneously adjusted for age, sex, and the comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis. Kaplan–Meier estimates were plotted to illustrate the cumulative incidence of osteoporosis, and the log-rank test was performed to examine the difference between the HCV exposure and the comparison cohorts. All statistical analyses were performed using the SAS package (Version 9.4 for Windows; SAS institute, Inc, Cary, NC). A 2-sided p value < .05 was considered statistically significant.

RESULTS
Of the 51,535 sampled patients, 41,228 and 10,307 were categorized as the comparison and HCV exposure cohorts, respectively (Table 1). Most patients were aged ≥50 years (61.7%), and 54.6% of the patients were women. The mean age was 54.1 ± 15.3 years in the HCV exposure cohort and 53.7 ± 15.5 years in the comparison cohort. Regarding baseline characteristics, the HCV exposure cohort exhibited a higher prevalence of diabetes, hypertension, hyperlipidemia, heart failure, stroke, obesity, and cirrhosis than did the comparison cohort. During the mean follow-up periods of 5.44 and 6.01 years for the HCV exposure and comparison cohorts, respectively, the Kaplan–Meier curve revealed that the cumulative incidence of osteoporosis was higher in the HCV exposure cohort than in the comparison cohort (Figure 1, log-rank test P < 0.001).

The overall incidence of osteoporosis in the HCV exposure cohort was higher than that in the comparison cohort (8.27 vs 6.19 per 1,000 person-years; crude HR = 1.33, 95% CI = 1.20–1.47) (Table 2). After we adjusted for factors such as age, sex, and comorbidities, namely diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis, the risk of developing osteoporosis was significantly higher in the HCV exposure cohort than in the comparison cohort (adjusted HR [aHR] = 1.35; 95% CI = 1.21–1.51). Compared with patients aged ≤49 years, the risk of developing osteoporosis was 4.05-fold higher in those aged 50 to 64 years (95% CI = 3.845–4.760) and 8.82-fold higher in those aged 65 years or older (95% CI = 7.48–10.40). In the multivariate model, the risk for osteoporosis was 3.10-fold higher for women than for men (95% CI = 2.81–3.43) and was higher for patients with the comorbidities of hypertension (aHR = 1.19,
to HCV in all stratifications was higher than that in the comparison cohorts. However, the risk of osteoporosis contributed by HCV decreased with age (aged \( \leq 49 \): aHR = 1.79, 95% CI = 1.32–2.43; aged 50–64: aHR = 1.36, 95% CI = 1.14–1.62; aged \( \geq 65 \): aHR = 1.23, 95% CI = 1.05–1.44) and the presence of comorbidity (no comorbidity: aHR = 1.54, 95% CI = 1.26–1.89; comorbidity: aHR = 1.27, 95% CI = 1.12–1.43).

The patients exposed to HCV exhibited a 1.38-fold (95% CI = 1.24–1.55) higher risk of developing osteoporosis compared with the patients who were not exposed to HCV (Table 4). The risk of osteoporotic fracture did not differ significantly between patients exposed to HCV and the comparison cohorts (aHR = 0.80, 95% CI = 0.44–1.45).

### DISCUSSION

Consistent with the literature proposing that HCV sero-prevalence peaks after age 55 and that women are predisposed to HCV infection, our results revealed that most patients (61.7%) were aged \( \geq 50 \) years and that 54.6% of the patients were women.\(^{22,23}\) The mean age in the HCV exposure cohort was 54.1 ± 15.3 years. Compared with patients who were not exposed to HCV, patients who were exposed to HCV tended to have more comorbidities, including diabetes, hypertension, hyperlipidemia, heart failure, stroke, obesity, and cirrhosis. Our results revealed that the HCV exposure cohort had more comorbidities; however, the risk of osteoporosis remained higher in the HCV exposure cohort after adjusting for age, sex, and the comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis. The mechanism affecting the pathophysiology that causes comorbidities in patients exposed to HCV may include HCV-associated insulin resistance and atherosclerosis.\(^{23}\) HCV may cause diabetes mellitus by directly interfering with insulin signaling and inducing insulin resistance in hepatocytes; HCV-infected hepatocytes can secrete mediators that induce extrahepatic insulin resistance and atherosclerosis.\(^{20}\) Estrogen deficiency and aging are the major etiologies of primary osteoporosis. Estrogen can protect against osteoporosis by inhibiting osteoblast apoptosis and increasing osteoblast lifespan.\(^{29,30}\) The decreasing rate of bone mineral density is swifter in the early postmenopausal period, which typically begins after age 50, and women aged 40 to 59 years have the highest risk of developing osteoporosis.\(^{23,30,31}\) Consistent with our result that women are predisposed to osteoporosis, the US Preventive Services Task Force indicated that as many as 1 in 2 postmenopausal women and 1 in 5 men are at risk for osteoporosis-related fracture.\(^{32}\)

Moreover, in the present study, osteoporosis was associated with hypertension, hyperlipidemia, and heart failure. Both osteoporosis and hypertension are common among the aging population and may share similar etiologies, such as low calcium intake and levels, vitamin D and vitamin K deficiency.

TABLE 1. Demographic Characteristics and Comorbidities in Cohorts With and Without HCV Exposure

| Variable          | No          | Yes         | P Value |
|-------------------|-------------|-------------|---------|
| Age, year         | N = 41228   | N = 10307   | 0.99    |
| \( \leq 49 \)     | 16,200(39.3)| 4050(39.3)  |         |
| 50–64             | 14,008(34.0)| 3502(34.0)  |         |
| 65+               | 11,020(26.7)| 2755(26.7)  |         |
| Mean ± SD\(^1\)   | 53.7(15.5)  | 54.1(15.3)  | 0.01    |
| Sex               |             |             | 0.99    |
| Female            | 18,700(45.4)| 4675(45.4)  |         |
| Male              | 22,528(54.6)| 5632(54.6)  |         |
| Comorbidity       |             |             |         |
| Diabetes          | 3779(9.17)  | 1690(16.4)  | <0.001  |
| Hypertension      | 13,731(33.3)| 4379(42.5)  | <0.001  |
| Hyperlipidemia    | 7931(19.2)  | 2496(24.2)  | <0.001  |
| Heart failure     | 1116(2.71)  | 494(4.79)   | <0.001  |
| Stroke            | 1617(3.92)  | 529(5.13)   | <0.001  |
| Obesity           | 147(0.36)   | 57(0.55)    | 0.005   |
| Cirrhosis         | 348(0.84)   | 1382(13.4)  | <0.001  |

HCV = hepatitis C virus, SD = standard deviation. Chi-Square test.

\(^1\)t-test.

95% CI = 1.07–1.31), hyperlipidemia (aHR = 1.17, 95% CI = 1.05–1.29), and heart failure (aHR = 1.23, 95% CI = 1.02–1.49).

The incidence of osteoporosis increased with age, was higher in women than in men, and increased with comorbidity in both cohorts (Table 3). The overall risk of osteoporosis related to several variables including age, sex, and presence of comorbidities was compared in the HCV exposure cohort and the comparison cohort. The risk of osteoporosis in patients exposed

FIGURE 1. Cumulative incidence comparison of osteoporosis for patients with (dashed line) or without (solid line) HCV exposure. HCV = hepatitis C virus.
high salt consumption, imbalanced nitric oxide levels, and antihypertensive agents that exert detrimental effects on the skeletal metabolism, strength, and density. Hyperlipidemia can reduce bone formation and promote bone loss by causing the products of lipid oxidation to accumulate in the subendothelial spaces of the vasculature and bone. Moreover, hyperlipidemia can induce secondary hyperparathyroidism, thereby impairing bone regeneration and mechanical strength. Heart failure and osteoporosis share several risk factors, such as aging, smoking, and postmenopausal and antihypertensive agents; heart failure can also accelerate bone loss by inducing hyperaldosteronism and secondary hyperparathyroidism. However, the effect of obesity on bone metabolism is controversial. Obesity is traditionally regarded as a protective factor for osteoporosis, conferring a positive mechanical loading on bone formation. Nevertheless, evidence supports the deteriorating effect of obesity on osteoporosis. For example, both osteoblasts and adipocytes are derived from a common mesenchymal stem cell and agents inhibiting adipogenesis-stimulated osteoblast differentiation and vice versa. Furthermore, the reduced bone formation caused by aging is usually accompanied by adipogenesis in bone marrow cavities. Moreover, elevated oxidative stress is common in people with obesity and osteoporosis. To our knowledge, this is the first population-based study to assess the relation between HCV exposure and the incidences of osteoporosis and osteoporotic fracture. Our statistical analyses benefited from the use of a nationwide database and the 12-year observation of participants selected from a representative cohort comprising 1,000,000 residents covered by the NHI program. Hansen et al conducted a large-scale population-based study to explore the association between HCV exposure and all-site fracture, but omitted discussing osteoporosis development. They concluded that the risk of fracture equally increased in patients exposed to HCV (chronic or cleared

| Variable          | Event  | PY       | Rate\(^1\) | Crude HR (95% CI)\(^2\) | Adjusted HR\(^3\) (95% CI) |
|-------------------|--------|----------|------------|--------------------------|----------------------------|
| HCV infection     | No     | 1534     | 247,886    | 6.19                     | 1.00                       | 1.00                       |
|                   | Yes    | 464      | 56,111     | 8.27                     | 1.33(1.20, 1.47)***         | 1.35(1.21, 1.51)***         |
| Age, year         | ≤ 49   | 198      | 132,967    | 1.49                     | 1.00                       | 1.00                       |
|                   | 50–64  | 731      | 103,325    | 7.07                     | 4.71(4.03, 5.51)***         | 4.05(3.45, 4.76)***         |
|                   | 65+    | 1069     | 67,705     | 15.8                     | 10.4(8.90, 12.1)***         | 8.82(7.48, 10.4)***         |
| Sex               | Female | 1456     | 137,743    | 10.6                     | 3.24(2.94, 3.58)***         | 3.10(2.81, 3.43)***         |
|                   | Male   | 542      | 166,254    | 3.26                     | 1.00                       | 1.00                       |
| Comorbidity       | Diabetes |        |            |                          |                            |                            |
|                   | No     | 1708     | 277,151    | 6.16                     | 1.00                       | 1.00                       |
|                   | Yes    | 290      | 26,846     | 10.8                     | 1.70(1.50, 1.93)***         | 0.91(0.80, 1.04)            |
| Hypertension      | No     | 880      | 208,129    | 4.23                     | 1.00                       | 1.00                       |
|                   | Yes    | 1118     | 95,868     | 11.7                     | 2.70(2.48, 2.95)***         | 1.19(1.07, 1.31)**          |
| Hyperlipidemia    | No     | 1358     | 247,148    | 5.49                     | 1.00                       | 1.00                       |
|                   | Yes    | 640      | 56,849     | 11.3                     | 2.02(1.84, 2.22)***         | 1.17(1.05, 1.29)**          |
| Heart failure     | No     | 1879     | 297,236    | 6.32                     | 1.00                       | 1.00                       |
|                   | Yes    | 119      | 6761       | 17.6                     | 2.66(2.21, 3.20)***         | 1.23(1.02, 1.49)*           |
| Stroke            | No     | 1879     | 294,877    | 6.37                     | 1.00                       | 1.00                       |
|                   | Yes    | 119      | 9120       | 13.1                     | 1.96(1.62, 2.35)***         | 1.03(0.85, 1.25)            |
| Obesity           | No     | 1989     | 302,976    | 6.56                     | 1.00                       | 1.00                       |
|                   | Yes    | 9        | 1021       | 8.82                     | 1.30(0.68, 2.50)            | -                          |
| Cirrhosis         | No     | 1914     | 297,566    | 6.43                     | 1.00                       | 1.00                       |
|                   | Yes    | 84       | 6431       | 13.1                     | 1.93(1.55, 2.40)***         | 1.21(0.96, 1.52)            |

CI = confidence interval, HCV = hepatitis C virus, HR = hazard ratio, PY = person-years.
\(^1\)Rate: incidence rate, per 1000 person-years
\(^2\)Crude HR: relative hazard ratio
\(^3\)Adjusted HR: multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis.
\(^*\)P < 0.05
\(^**\)P < 0.01
\(^***\)P < 0.001.
Several pathogenic mechanisms are involved in bone mineral density loss in patients exposed to HCV. First, fibronectin can infiltrate the bone matrix to enhance matrix mineralization, reducing its production by the liver. However, oncofetal fibronectin increases and can directly inhibit osteoblast function. Second, insulin-like growth factor 1, involved in osteoblast differentiation and proliferation, is produced by the liver and is reduced in patients with chronic liver disease. Third, the receptor--activator ratio of nuclear factor kappa ligand and osteoprotegerin is higher in patients with chronic liver disease, which can directly inhibit osteoclast activity. Fourth, interleukin-6 is increased by HCV on osteoporotic fracture was not obvious. By contrast, the association between HCV and osteoporosis may be due to shared risk factors since the prevalence of osteoporosis-associated lifestyle factors could not be investigated in this study. However, potential osteoporosis-associated comorbidities were confounded in our study. Third, validating the diagnosis of osteoporosis or osteoporotic fracture has been thoroughly documented. Second, osteoporosis-associated lifestyle factors could not be investigated in this study. However, we excluded patients with important comorbidities at baseline also confirmed the validity of our results. This finding, coupled with the results of the subgroup analyses, affirms the possible causal association between HCV and osteoporosis, and suggests that HCV may be a possible risk factor for osteoporosis. Nevertheless, HCV may be less influential than other risk factors, such as hypertension, hyperlipidemia, and heart failure, in contributing to the development of osteoporosis.

The present study had some strength. First, the large-scale national database provided statistical benefits to our longitudinal study to evaluate the association between HCV and osteoporosis. Second, the recruited subjects were a stable population with the results of the subgroup analyses, affirms the possible causal association between HCV and osteoporosis, and suggests that HCV may be a possible risk factor for osteoporosis. Nevertheless, HCV may be less influential than other risk factors, such as hypertension, hyperlipidemia, and heart failure, in contributing to the development of osteoporosis.

### Table 3: Incidence of Osteoporosis by Age, Sex, and Comorbidity and Cox Model Measured Hazards Ratio for Patients With HCV Infection Compared Those Without HCV Exposure

| Variables | HCV Exposure | Rate | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-----------|--------------|------|------------------|---------------------|
| Age, years | No | Yes | | |
| ≤ 49 | 134 | 64 | 1.25 | 1.98 (1.47, 2.67)* | 1.79 (1.32, 2.43)*** |
| 50–64 | 554 | 177 | 6.56 | 1.42 (1.20, 1.68)*** | 1.36 (1.14, 1.62)*** |
| 65+ | 846 | 223 | 15.0 | 1.29 (1.11, 1.49)*** | 1.23 (1.05, 1.44)* |
| Sex | Female | 1129 | 327 | 12.7 | 1.25 (1.10, 1.41)* | 1.30 (1.14, 1.48)*** |
| Male | 405 | 137 | 2.98 | 4.51 | 1.51 (1.24, 1.83)*** | 1.51 (1.23, 1.84)*** |
| Comorbidity | No | Yes | | |
| | 507 | 350 | 3.40 | 4.32 | 1.27 (1.04, 1.55)* | 1.54 (1.26, 1.89)*** |
| | 1007 | 929 | 10.8 | 11.8 | 1.08 (0.95, 1.22) | 1.27 (1.12, 1.43)*** |

CI = confidence interval, HCV = hepatitis C virus, HR = hazard ratio, PY = person-years.

Comorbidity: patients with any 1 of the comorbidities diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis were classified as the comorbidity group.

Rate: incidence rate, per 1000 person-years.

Crude HR: relative hazard ratio.

Adjusted HR: multivariable analysis including age, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis.

* P < 0.05.

** P < 0.01.

*** P < 0.001.
exposure and osteoporosis since the date of HCV exposure could not be ascertained.

In conclusion, this nationwide population-based cohort study concludes that HCV exposure increases the risk of developing subsequent osteoporosis, but no detrimental effect on osteoporotic fracture was observed. Furthermore, HCV may be less influential than other risk factors, such as hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis, in contributing to the development of osteoporosis.

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**TABLE 4. Comparisons of Hazard Ratios Between Patients With and Without HCV Exposure for Different Outcomes Osteoporosis (or Osteoporotic Fracture)**

| Variables (ICD-9-CM) | Event | Rate | Crude HR (95% CI) | Adjusted HR (95% CI) |
|----------------------|-------|------|------------------|---------------------|
| Osteoporosis         |       |      |                  |                     |
| Without HCV exposure | 1457  | 5.88 | 1 (Reference)    | 1 (Reference)       |
| With HCV exposure    | 449   | 8.00 | 1.35 (1.21, 1.50) | 1.38 (1.24, 1.55)   |
| Osteoporotic fracture|       |      |                  |                     |
| Without HCV exposure | 77    | 0.31 | 1 (Reference)    | 1 (Reference)       |
| With HCV exposure    | 15    | 0.27 | 0.86 (0.50, 1.50) | 0.80 (0.44, 1.45)   |

CI = confidence interval, HCV = hepatitis C virus, HR = hazard ratio.

1 Rate: incidence rate, per 1000 person-years

2 Crude HR: relative hazard ratio

3 Adjusted HR: multivariable analysis including age, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis.

4 **P < 0.001.**
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