

# 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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**Abbreviations:** aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, HCV = hepatitis C virus, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, LHID2000 = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, SD = standard deviation.

## 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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3–5</sup> Furthermore, it is reported that asymptomatic vertebral fractures are associated with future hip fracture by threefold and other nonvertebral fracture by twofold.<sup>6</sup> 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.<sup>3</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>3,9,10</sup>

Hepatitis C virus infection (HCV) is a global health problem estimated to affect 170 million people worldwide.<sup>11</sup> Hepatitis C virus infection is a hepatotropic virus that mainly

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causes inflammation and fibrosis of the liver. It is reported that ~20% of HCV-infected patients will progress to liver cirrhosis.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup> Some scholars have proposed that chronic HCV infection without liver cirrhosis contributes to reduced bone mineral density, whereas other scholars have asserted the opposite.<sup>15–20</sup>

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.<sup>21</sup> 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:m 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  $\geq 50$  years (61.7%), and 54.6% of the patients were women. The mean age was  $54.1 \pm 15.3$  years in the HCV exposure cohort and  $53.7 \pm 15.5$  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  $\leq 49$  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,

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

Variable	HCV Exposure		P Value
	No N = 41228	Yes N = 10307	
Age, year			0.99
≤ 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 <sup>†</sup>	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.  
<sup>†</sup> 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

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 ≤ 49: aHR = 1.79, 95% CI = 1.32–2.43; aged 50–64: aHR = 1.36, 95% CI = 1.14–1.62; aged ≥ 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).

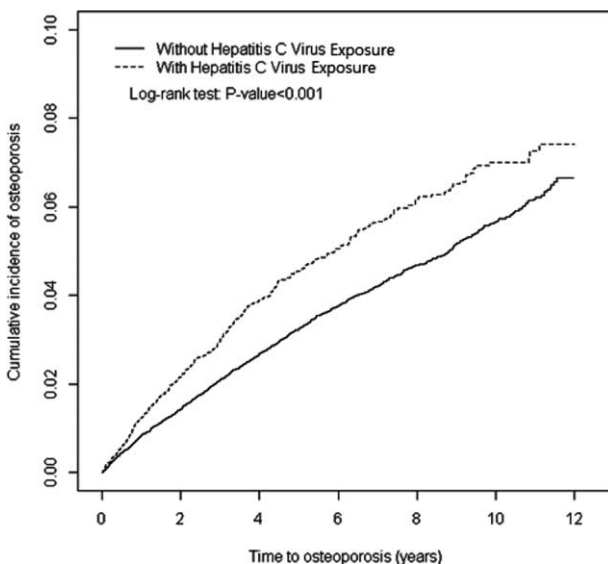
The patients exposed to HCV exhibited a 1.38-fold (95% CI = 1.24–1.55) higher risk of developing osteoporosis compared with the patients who were not exposed to HCV (Table 4). The risk of osteoporotic fracture did not differ significantly between patients exposed to HCV and the comparison cohorts (aHR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

**DISCUSSION**

Consistent with the literature proposing that HCV seroprevalence peaks after age 55 and that women are predisposed to HCV infection, our results revealed that most patients (61.7%) were aged ≥50 years and that 54.6% of the patients were women.<sup>22,23</sup> 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.<sup>13</sup> 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, notably in the skeletal muscle. Hepatitis C virus may increase the risk of cardiovascular and cerebrovascular events through atherosclerosis induced by systemic inflammation, chronic endothelial injury, or direct infection of the arterial wall.<sup>24–26</sup>

Our study revealed that the osteoporosis incidence increased with age and was higher in women than in men. The association between osteoporosis and aging has been confirmed in the literature, and the gene expression of the rennin–angiotensin system independent of hypertension in the skeletal tissue may contribute to osteoporosis.<sup>27,28</sup> Estrogen deficiency and aging are the major etiologies of primary osteoporosis. Estrogen can protect against osteoporosis by inhibiting osteoblast apoptosis and increasing osteoblast lifespan.<sup>29,30</sup> 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.<sup>23,30,31</sup> 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.<sup>32</sup>

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,



**FIGURE 1.** Cumulative incidence comparison of osteoporosis for patients with (dashed line) or without (solid line) HCV exposure. HCV = hepatitis C virus.

**TABLE 2.** The Incidence and Hazard ratio for Osteoporosis and Osteoporosis-Associated Risk Factor

Variable	Event	PY	Rate <sup>†</sup>	Crude HR (95% CI) <sup>‡</sup>	Adjusted HR <sup>§</sup> (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) <sup>***</sup>	1.35(1.21, 1.51) <sup>***</sup>
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) <sup>***</sup>	4.05(3.45, 4.76) <sup>***</sup>
65+	1069	67,705	15.8	10.4(8.90, 12.1) <sup>***</sup>	8.82(7.48, 10.4) <sup>***</sup>
Sex					
Female	1456	137,743	10.6	3.24(2.94, 3.58) <sup>***</sup>	3.10(2.81, 3.43) <sup>***</sup>
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) <sup>***</sup>	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) <sup>***</sup>	1.19(1.07, 1.31) <sup>**</sup>
Hyperlipidemia					
No	1358	247,148	5.49	1.00	1.00
Yes	640	56,849	11.3	2.02(1.84, 2.22) <sup>***</sup>	1.17(1.05, 1.29) <sup>**</sup>
Heart failure					
No	1879	297,236	6.32	1.00	1.00
Yes	119	6761	17.6	2.66(2.21, 3.20) <sup>***</sup>	1.23(1.02, 1.49) <sup>*</sup>
Stroke					
No	1879	294,877	6.37	1.00	1.00
Yes	119	9120	13.1	1.96(1.62, 2.35) <sup>***</sup>	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) <sup>***</sup>	1.21(0.96, 1.52)

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

<sup>†</sup> Rate: incidence rate, per 1000 person-years

<sup>‡</sup> Crude HR: relative hazard ratio

<sup>§</sup> Adjusted HR: multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis.

<sup>\*</sup>  $P < 0.05$ .

<sup>\*\*</sup>  $P < 0.01$ .

<sup>\*\*\*</sup>  $P < 0.001$ .

high salt consumption, imbalanced nitric oxide levels, and antihypertensive agents that exert detrimental effects on the skeletal metabolism, strength, and density.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35</sup> However, the effect of obesity on bone metabolism is controversial.<sup>36</sup> 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.<sup>15–20</sup> 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

**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						Crude HR <sup>‡</sup> (95% CI)	Adjusted HR <sup>§</sup> (95% CI)
	No			Yes				
	Event	PY	Rate <sup>†</sup>	Event	PY	Rate <sup>†</sup>		
Age, years								
≤ 49	134	10,7198	1.25	64	25,769	2.48	1.98(1.47, 2.67) <sup>***</sup>	1.79(1.32, 2.43) <sup>***</sup>
50–64	554	84,389	6.56	177	18,935	9.35	1.42(1.20, 1.68) <sup>***</sup>	1.36(1.14, 1.62) <sup>***</sup>
65+	846	56,298	15.0	223	11,407	19.6	1.29(1.11, 1.49) <sup>***</sup>	1.23(1.05, 1.44) <sup>*</sup>
Sex								
Female	1129	112,022	10.1	327	25,721	12.7	1.25(1.10, 1.41) <sup>***</sup>	1.30(1.14, 1.48) <sup>***</sup>
Male	405	135,864	2.98	137	30,390	4.51	1.51(1.24, 1.83) <sup>***</sup>	1.51(1.23, 1.84) <sup>***</sup>
Comorbidity <sup>  </sup>								
No	507	154,924	3.40	114	26,366	4.32	1.27(1.04, 1.55) <sup>*</sup>	1.54(1.26, 1.89) <sup>***</sup>
Yes	1007	92,961	10.8	350	29,745	11.8	1.08(0.95, 1.22)	1.27(1.12, 1.43) <sup>***</sup>

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

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

<sup>†</sup> Rate: incidence rate, per 1000 person-years

<sup>‡</sup> Crude HR: relative hazard ratio;

<sup>§</sup> Adjusted HR: multivariable analysis including age, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis.

<sup>\*</sup>  $P < 0.05$ .

<sup>\*\*</sup>  $P < 0.01$ .

<sup>\*\*\*</sup>  $P < 0.001$ .

infections), and the major determinants of fracture in such patients are lifestyle-related factors, such as alcohol and drug abuse, which substantially increases fracture risk.<sup>20</sup> By contrast, our epidemiological study demonstrated that HCV exposure increases the risk of osteoporosis and the detrimental effect of HCV on osteoporotic fracture was not obvious.

Several pathogenic mechanisms are involved in bone mineral density loss in patients exposed to HCV.<sup>37</sup> 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, enhancing bone resorption. Fourth, interleukin-6 is increased by chronic HCV infection and can activate osteoclasts to increase bone resorption. Fifth, hypogonadism in chronic liver disease can result in increased osteoclast activity. Finally, bilirubin elevation can inhibit in vitro osteoblast proliferation.<sup>38</sup>

By contrast, the association between HCV and osteoporosis may be due to shared risk factors since the prevalence of important osteoporosis risk factors was higher in the HCV exposed patients as compared to the patients without HCV exposure. However, it is reasonable to conclude that the increased risk of osteoporosis observed in HCV exposed patients was more likely to be due to the effect of their HCV status since the possible confounding effect of osteoporosis risk factors has been significantly minimized in our study. Moreover, the osteoporosis risk contributed by HCV decreased with the increment of age may be due to the absence or low prevalence of osteoporosis-associated comorbidities in the younger patients. The results of our subgroup analyses in which

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 suggested 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 and ~99% of the residents in Taiwan have been covered by the NHI program. Nevertheless, our study had several limitations. First, we could not ascertain the patients' viremic status, such as the viral loads or the genotypes of the HCV. Nevertheless, all patients in our case cohort exhibited positive anti-HCV antibodies, which mean recent or past HCV exposure. Moreover, the effect of antiviral therapy on the stage of liver fibrosis or the grade of liver inflammation could not be ascertained in our study. Therefore, we could not prove the ameliorating effect of antiviral therapy on bone mineral density through the arrest of liver cirrhosis even though the association between osteoporotic fracture and cirrhosis has been thoroughly documented. Second, 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 was difficult. However, to enhance the accuracy of diagnosis, we only recruited patients who received medical care for osteoporosis >3 separate visits. Moreover, the BNHI organizes regular audits performed by medical experts to ensure the accuracy of insurance claim codes in Taiwan. Finally, we cannot clarify the temporal association between HCV

**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 <sup>†</sup>	Crude HR <sup>‡</sup> (95% CI)	Adjusted HR <sup>§</sup> (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.

<sup>†</sup> Rate: incidence rate, per 1000 person-years

<sup>‡</sup> Crude HR: relative hazard ratio

<sup>§</sup> Adjusted HR: multivariable analysis including age, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, stroke, and cirrhosis.

\*\*\*  $P < 0.001$ .

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, and heart failure, in contributing to the development of osteoporosis.

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