



The association between hepatitis and osteoporosis: a nested case-control study using a national sample cohort

Chanyang Min^{1,2,3} · Woo Jin Bang⁴ · Miyoung Kim⁵ · Dong Jun Oh⁶ · Hyo Geun Choi^{1,2}

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Abstract

Summary The prevalence of hepatitis B was higher in osteoporosis patients than the control group, especially in females. However, the prevalence of hepatitis C was not different. The matching for various factors improved to have same conditions between osteoporosis patients and the control group.

Purpose Although chronic liver disease, including hepatitis B and hepatitis C, has been associated with osteoporosis in previous studies, the evidence was insufficient, and some findings were inconsistent. The aim of this study was to evaluate the relationship between hepatitis B or hepatitis C and osteoporosis.

Methods We used the Korean National Health Insurance Service-National Sample Cohort with ≥ 50 -year-old participants from 2002 to 2013. Age was determined at osteoporosis diagnosis. We extracted 68,492 osteoporosis patients (ICD-10 codes E7001–E7004, HC341–HC345) with a 68,492-member control group at a ratio of 1:1 by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. We analyzed previous histories of hepatitis B (ICD-10 codes B18.0–B18.1) and hepatitis C (ICD-10 code B18.2) in the osteoporosis patients and control groups. The logistic regression with the crude and adjusted model was analyzed. Additionally, subgroup analyses divided by age and sex were performed.

Results The adjusted odds ratios for hepatitis B and hepatitis C were 1.19 (95% confidence interval (CI) = 1.11–1.28, $P < 0.001$) and 1.04 (95% CI = 0.90–1.19, $P > 0.05$), respectively, in osteoporosis patients. Subgroup analyses showed that the risk of hepatitis B was higher in osteoporosis patients in female groups but not in male groups.

Conclusion Hepatitis B virus infection might be a risk factor for osteoporosis.

Keywords Hepatitis B · Hepatitis C · Infection · Liver disease · Osteoporosis · Bone loss

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✉ Hyo Geun Choi
pupen@naver.com

- ¹ Hallym Data Science Laboratory, Hallym University College of Medicine, Anyang, South Korea
- ² Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, Anyang, South Korea
- ³ Graduate School of Public Health, Seoul National University, Seoul, South Korea
- ⁴ Department of Urology, Hallym University College of Medicine, Anyang, South Korea
- ⁵ Department of Laboratory Medicine, Hallym University College of Medicine, Anyang, South Korea
- ⁶ Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Introduction

Both hepatitis B and hepatitis C are global health problems caused by infection with hepatitis B virus and hepatitis C virus, respectively. Worldwide, the prevalence of hepatitis B is approximately 6%, and the prevalence of hepatitis C is 1.5 to 2.3% [1, 2]. In Korea, the prevalence of hepatitis B is 2.9%, and the prevalence of hepatitis C is 0.6 to 0.8% [3, 4]. Both viral infections can lead to acute or chronic liver disease, such as cirrhosis and hepatocellular carcinoma. Moreover, hepatitis B and hepatitis C can cause death through impaired liver function [1, 2].

Osteoporosis is characterized by low bone mass and deterioration of bone tissue, thus increasing bone fragility and fracture risk [5]. Osteoporosis is the most common bone disease worldwide. Moreover, this bone disease is an enormous economic burden for both the medical field and aging individuals, including postmenopausal women [6]. In the USA, the prevalence of osteoporosis in people ≥ 50 years old was

16.0% in men and 29.9% in women [7]. In Korea, the prevalence was estimated as 7.5% and 37.3% in ≥ 50 -year-old men and women, respectively [8]. Lack of sex steroids, calcium and vitamin D insufficiency, and aging are known risk factors for osteoporosis [6].

Increasing evidence has demonstrated that chronic liver disease is associated with osteoporosis [9]. One of the linking mechanisms between chronic liver disease and osteoporosis was impaired liver function, such as dysfunction of vitamin D absorption [10, 11]. Some studies have suggested that hepatitis B or hepatitis C infection is independently associated with osteoporosis [12–19]. However, the studies were few, and some outcomes were inconsistent [20, 21].

The purpose of our study was to investigate the association between hepatitis B or hepatitis C and osteoporosis. In our study, we conducted a nested case-control study design using a large and representative national sample cohort in Korea. Moreover, osteoporosis patients were matched at a 1:1 ratio with the control group by various confounding factors to achieve the same conditions between osteoporosis patients and the control group. Furthermore, we analyzed an adjusted model not only for demographic variables but also for health-related risks, such as dyslipidemia, diabetes mellitus, hypertension, ischemic heart disease, stroke, depression, and liver cirrhosis.

Materials and methods

Study population and data collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. The requirement for written informed consent was waived by the Institutional Review Board.

This national cohort study relied on data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The Korean National Health Insurance Service (NHIS) selects samples directly from the entire population database to prevent nonsampling errors. Approximately 2% of the samples (one million) were selected from the entire Korean population (50 million). These selected data can be classified according to 1476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. After data selection, the appropriateness of the sample was verified by a previous study [22]. The details of the methods used to perform these procedures are provided by the National Health Insurance Sharing Service [23]. This cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes using the International Classification of Disease-10 (ICD-

10), (iv) death records from the Korean National Statistical Office (using the Korean Standard Classification of Disease), (v) socioeconomic data (residence and income), and (vi) medical examination data for each participant over a period ranging from 2002 to 2013.

Because all Korean citizens are identified by a 13-digit resident registration number from birth to death, exact population statistics can be determined using this database. Enrollment in the NHIS is mandatory for all Koreans. All Korean hospitals and clinics use these 13-digit resident registration numbers to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. Moreover, all medical treatments in Korea can be tracked without exception using the Health Insurance Review & Assessment (HIRA) system. In Korea, notice of death to an administrative entity is legally required before a funeral can be held. Causes and the date of death are recorded by medical doctors on a death certificate.

Participant selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed with osteoporosis. Osteoporosis was defined using the ICD-10 codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in diseases classified elsewhere) from 2002 through 2013. Among them, we selected the participants who were treated for it ≥ 2 times or participants who were diagnosed with osteoporosis by bone density test using X-ray or CT (claim code E7001–E7004, HC341–HC345) ($n = 94,912$).

Hepatitis infection was included if the participant was diagnosed using the following ICD-10 codes: chronic viral hepatitis B with delta-agent (B18.0), chronic viral hepatitis B without delta-agent (B18.1), and chronic viral hepatitis C (B18.2). A total of 38,691 hepatitis B and 7584 hepatitis C participants were included.

The osteoporosis patients were matched at a 1:1 ratio with patients (control group) in this cohort who were never treated for osteoporosis from 2002 through 2013. The control group was selected from the original population ($n = 1,030,779$). These subjects were matched for age, group, sex, income, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent a selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from top to bottom. The matched control participants were assumed to be involved at the same time as each matched osteoporosis participant (index date). Therefore, the control group subjects who died before the index date were excluded. Osteoporosis patients for whom we could not identify enough matched participants were excluded ($n = 11,781$).

We also excluded participants aged less than 50 years ($n = 14,639$). Finally, 1:1 matching resulted in the inclusion of 68,492 osteoporosis patients and 68,492 control participants (Fig. 1). However, they were not matched for ischemic heart disease, cerebral stroke, depression, and liver cirrhosis because strict matching increases the number of excluded study participants due to a lack of control participants. After matching, we analyzed the participants' previous histories of hepatitis B and hepatitis C infection in both the osteoporosis and control groups.

Variables

The age groups were classified using 5-year intervals as follows: 50–54, 55–59, 60–64 ..., and 85+ years old. Age was determined at osteoporosis diagnosis. A total of eight age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employed health insurance classes, and 20 employed health insurance classes). These groups were recategorized into five classes (class 1 [lowest income]–class 5 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of the participants were evaluated using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10–E14), and dyslipidemia (E78) were assessed if the participants were treated ≥ 2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60–I66) were assessed if the participants were treated ≥ 1 time. Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times. Liver cirrhosis (K74) was assessed if the participants were treated ≥ 2 times.

Statistical analyses

Chi-squared tests were used to compare the general characteristics between the osteoporosis and control groups.

To analyze the odds ratio (OR) of hepatitis B and hepatitis C with osteoporosis, unconditional logistic regression analysis was used. In this analysis, crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression) models were used, and 95% confidence intervals (CIs) were calculated.

For the subgroup analyses, we divided the participants by age and sex (< 65 years old, and ≥ 65 years; males and females). This analysis was performed only in hepatitis B patients.

Fig. 1 Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 68,492 osteoporosis patients were matched with 68,492 control participants with respect to age, sex, income, region of residence, and past medical history of hypertension, diabetes mellitus, and dyslipidemia

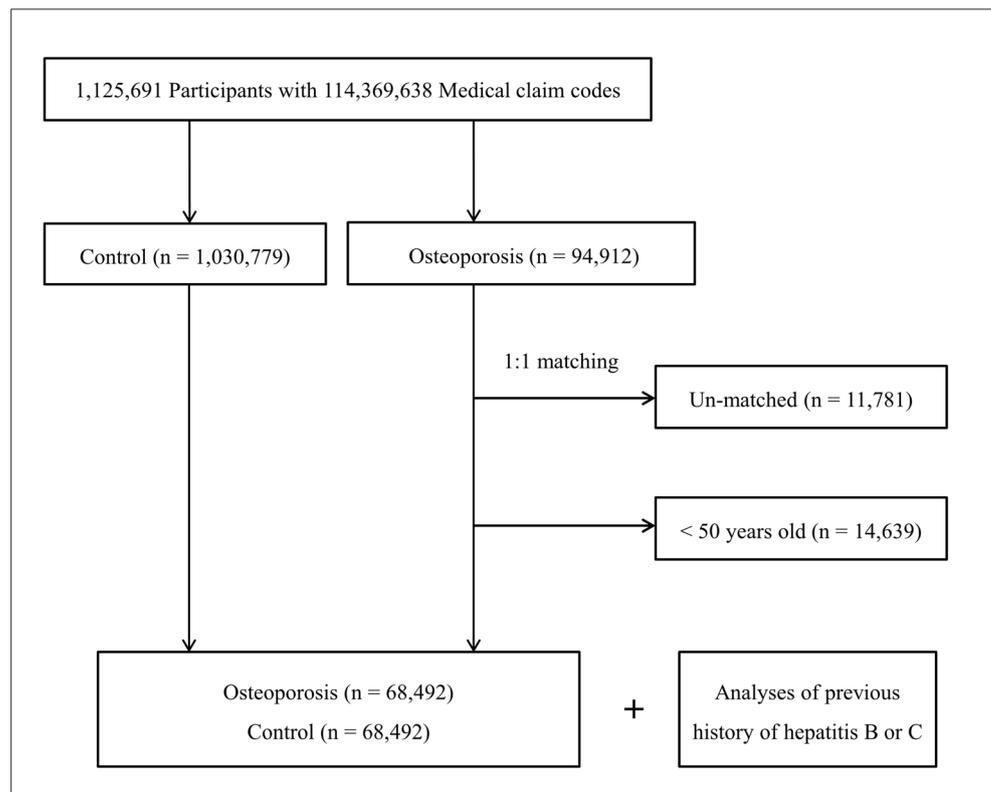


Table 1 General characteristics of participants

Characteristics	Total participants		P value
	Osteoporosis (n, %)	Control group (n, %)	
Age (years old)			1.000
50–54	12,797 (18.7)	12,797 (18.7)	
55–59	12,491 (18.2)	12,491 (18.2)	
60–64	12,505 (18.3)	12,505 (18.3)	
65–69	11,125 (16.2)	11,125 (16.2)	
70–74	8508 (12.4)	8508 (12.4)	
75–79	5823 (8.5)	5823 (8.5)	
80–84	3261 (4.8)	3261 (4.8)	
85+	1982 (2.9)	1982 (2.9)	
Sex			1.000
Male	9740 (14.2)	9740 (14.2)	
Female	58,752 (85.8)	58,752 (85.8)	
Income			1.000
1 (Lowest)	13,617 (19.9)	13,617 (19.9)	
2	9167 (13.4)	9167 (13.4)	
3	10,740 (15.7)	10,740 (15.7)	
4	14,312 (20.9)	14,312 (20.9)	
5 (Highest)	20,656 (30.2)	20,656 (30.2)	
Region of residence			1.000
Urban	30,122 (44.0)	30,122 (44.0)	
Rural	38,370 (56.0)	38,370 (56.0)	
Hypertension			1.000
Yes	39,961 (58.3)	39,961 (58.3)	
No	28,531 (41.7)	28,531 (41.7)	
Diabetes			1.000
Yes	19,170 (28.0)	19,170 (28.0)	
No	49,322 (72.0)	49,322 (72.0)	
Dyslipidemia			1.000
Yes	25,049 (36.6)	25,049 (36.6)	
No	43,443 (63.4)	43,443 (63.4)	
Ischemic heart disease			<0.001*
Yes	7362 (10.7)	6220 (9.1)	
No	61,130 (89.3)	62,272 (90.9)	
Cerebral stroke			<0.001*
Yes	13,391 (19.6)	12,017 (17.5)	
No	55,101 (80.4)	56,475 (82.5)	
Depression			<0.001*
Yes	10,442 (15.2)	6988 (10.2)	
No	58,050 (84.8)	61,504 (89.8)	
Liver cirrhosis			0.005*
Yes	950 (1.4)	833 (1.2)	
No	67,542 (98.6)	67,659 (98.8)	
Hepatitis B			<0.001*
Yes	1853 (2.7)	1522 (2.2)	
No	66,639 (97.3)	66,970 (97.8)	
Hepatitis C			0.177
Yes	417 (0.6)	379 (0.6)	
No	68,075 (99.4)	68,113 (99.4)	

*Chi-squared test. Significance at $P < 0.05$

Two-tailed analyses were conducted, and P values < 0.05 were considered to indicate significance. The results were analyzed using SPSS v. 22.0 (IBM, Armonk, NY, USA).

Results

The rate of hepatitis B was higher in the osteoporosis patients (2.7% [1853/68,492]) than in the control group (2.2%

[1522/68,492], $P < 0.001$, Table 1). On the other hand, the rate of hepatitis C was not higher in the osteoporosis patients (0.6% [417/68,492]) than in the control group (0.6% [379/68,492], $P = 0.177$). The general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia) of the participants were exactly the same due to matching ($P = 1.000$). The rates of ischemic heart disease, cerebral stroke, depression, and liver cirrhosis were higher in the osteoporosis patients (each $P < 0.05$).

The adjusted ORs for hepatitis B and hepatitis C were 1.19 (95% CI = 1.11–1.28, $P < 0.001$) and 1.04 (95% CI = 0.90–1.19, $P > 0.05$) in the osteoporosis patients, respectively (Table 2).

In the subgroup analyses, the crude and adjusted ORs of osteoporosis patients in female groups for hepatitis B were higher than those of the control groups (each $P < 0.01$, Table 3). The adjusted OR was 1.18 (95% CI = 1.08–1.30) in the < 65 -year-old female group and 1.28 (95% CI = 1.09–1.50) in the ≥ 65 -year-old female group. The OR for hepatitis B was not significantly different between osteoporosis patients in male groups and control groups (each $P > 0.1$).

Discussion

We identified that the ORs for hepatitis B in osteoporosis patients were higher than in the control group, whereas the ORs for hepatitis C were not significantly different between osteoporosis patients and the control group. In subgroup analyses, the ORs for hepatitis B were higher in both the < 65 and ≥ 65 -year-old female groups with osteoporosis than in the control group but not in the male groups.

Our study outcomes are partially consistent with previous studies. Although some studies reported that hepatitis C was associated with bone-related markers [16–19], Pelazas-Gonzalez et al. reported that hepatitis C infection was not associated with bone mineral density [24]. On the other hand, previous studies reported that hepatitis B was associated with osteoporosis. In a cross-sectional study by Beag et al., bone mineral density in the femoral neck (seropositive = 0.810 g/cm², seronegative = 0.831 g/cm², $P = 0.032$) and lumbar spine (seropositive = 0.953 g/cm², seronegative = 0.974 g/cm², $P = 0.049$) was significantly lower in males who were hepatitis B seropositive [12]. In a case-control study by Huang et al., a higher prevalence of osteoporosis in the lumbar spine (prevalence of osteoporosis in hepatitis B patients = 12.8%, healthy control group = 4.7%, $P = 0.022$), total hip (prevalence of osteoporosis in hepatitis B patients = 11.5%, healthy control group = 4.1%, $P = 0.028$), and femoral neck (prevalence of osteoporosis in hepatitis B patients = 12.2%, healthy control group = 4.7%, $P = 0.035$) was associated with hepatitis B [15]. In a cohort study by Chen et al., the hazard ratio (HR) for osteoporosis was 1.14 (95% CI = 1.03–1.25, $P < 0.01$) in

Table 2 Crude and adjusted odd ratios (95% confidence interval) of osteoporosis for hepatitis B and C

Characteristics	Hepatitis B				Hepatitis C			
	Crude	<i>P</i> value	Adjusted ^a	<i>P</i> value	Crude	<i>P</i> value	Adjusted ^a	<i>P</i> value
Osteoporosis	1.22 (1.14–1.31)	< 0.001*	1.19 (1.11–1.28)	< 0.001*	1.10 (0.96–1.27)	0.177	1.04 (0.90–1.19)	0.616
Control	1.00		1.00		1.00		1.00	

^a Adjusted model for age, sex, income, region of residence, hypertension, diabetes, hyperlipidemia, ischemic heart disease, cerebral stroke, depression, and liver cirrhosis histories

*Logistic regression model, significance at $P < 0.05$

hepatitis B virus infection patients [14]. Another cohort study by Byrne et al. reported that untreated chronic hepatitis B patients in black persons had a higher HR for hip fracture than uninfected black persons (adjusted HR = 2.55, 95% CI = 1.42–4.58) [13]. Our study used a large, representative nationwide cohort with a large number of patients with osteoporosis. Moreover, we conducted a nested case-control study design, which reduces biases, such as recall bias of exposure and selection bias of control participants.

The linking mechanism between hepatitis B and osteoporosis is not fully understood. Instead, two potential mechanisms were suggested in the previous studies [13, 14]. Although, the role of osteoprotegerin and RANKL in the hepatic osteodystrophy is not clarified [25, 26], some previous studies suggested that inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1, and IL-6, induced by chronic liver disease are one of the potential linking mechanisms between hepatitis B and osteoporosis [27, 28]. These inflammatory cytokines increase receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibit osteoprotegerin

expression in human osteoblasts [29]. Moreover, TNF- α is known to inhibit osteoblast differentiation and promote osteoblast apoptosis. Eventually, bone mineral density decreases because of decreased bone formation and increased bone resorption [20, 21].

Another potential linking factor between hepatitis B and osteoporosis is impaired liver function by developing liver disease. For example, when insulin-like growth factor 1 is impaired by a decompensated liver, promotion osteoblast differentiation and proliferation is also impaired [30]. Moreover, a decompensated liver also decreases blood levels of testosterone and estrogen. These hormones activate osteoclasts and lead to bone loss [31]. In addition, because liver disease impairs the function of lipid absorption in the liver, vitamin D absorption also decreases, affecting bone loss [10, 11].

Although previous studies reported that hepatitis C was associated with osteoporosis [16, 18, 19], the association was not shown in our study. The outcomes were consistent in subgroup analyses (S1 Table). Because we extracted osteoporosis patients first, the prevalence of hepatitis C was low

Table 3 Subgroup analysis of crude and adjusted odd ratios (95% confidence interval) of osteoporosis for hepatitis B according to age and sex

Characteristics	Hepatitis B			
	Crude	<i>P</i> value	Adjusted ^a	<i>P</i> value
Age < 65 years old, males ($n = 5620$)				
Osteoporosis	1.36 (1.06–1.74)	0.017*	1.22 (0.94–1.58)	0.132
Control	1.00		1.00	
Age < 65 years old, females ($n = 69,966$)				
Osteoporosis	1.20 (1.10–1.31)	< 0.001*	1.18 (1.08–1.30)	< 0.001*
Control	1.00		1.00	
Age ≥ 65 years old, males ($n = 13,860$)				
Osteoporosis	1.21 (0.99–1.47)	0.068	1.11 (0.91–1.37)	0.313
Control	1.00		1.00	
Age ≥ 65 years old, females ($n = 47,538$)				
Osteoporosis	1.28 (1.09–1.49)	0.002*	1.28 (1.09–1.50)	0.003*
Control	1.00		1.00	

^a Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, depression, and liver cirrhosis histories

*Logistic regression analyses, significance at $P < 0.05$

(0.6%). In fact, the prevalence of hepatitis C in Korea is less than 1% [4]. Moreover, if the patients with hepatitis C were well treated by antiviral drugs, the bone loss would possibly be prevented [32]. Similarly, Pelazas-González et al. reported that hepatitis C virus in well-treated patients was not associated with the risk of osteoporosis [24]. In addition, Gaudio et al. reported that the occurrence of hepatitis C was affected by the measurement of bone mineral density. Specifically, although the measurement of dual-energy X-ray absorptiometry (DXA) was not associated with chronic liver disease associated with hepatitis C, the peripheral quantitative computed tomography (pQCT) and volumetric parameter measurements were associated with chronic liver disease [17]. However, the data for bone mineral density measurement are unknown in our study because of the use of secondary data. Therefore, the association between hepatitis C and osteoporosis is not clear in our study.

Our findings showed an association between female patients with osteoporosis and hepatitis B. However, a cross-sectional study by Beag et al. using a Korean population reported that only male groups had a positive association between hepatitis B and osteoporosis [12]. Because our study design was a nested case-control study, we first selected osteoporosis patients. Because the prevalence of osteoporosis is higher in females than males, the outcomes might not be clear due to the small sample sizes of male participants.

The main strength of our study is the use of a large, representative, and nationwide Korean population-based cohort. In addition, the participants were followed up during a long period without missing data. Because of these factors, we could randomly select a control group using 1:1 matching for age, sex, income, region of residence, and past medical history. Because of the large sample size, we could investigate the subgroup analysis. Furthermore, we used an adjusted model with various factors to minimize confounding effects. Specifically, we used the past medical histories including hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and liver cirrhosis as covariates because these diseases are associated with osteoporosis and liver disease [33, 34]. We also added depression as covariate because depression could alter immune response in patient with chronic diseases [35].

Our study has several limitations. First, because we used secondary data, the study was limited for our investigation purposes. For example, we could not investigate the Child-Pugh score or specific level of bone loss from participants. In addition, we could not distinguish and adjust the menopause status in female participants. Moreover, we could not control for other possible lifestyle factors between hepatitis and osteoporosis, such as obesity, smoking, drug intake, vitamin D supplementation, dietary habits including alcohol intake, and sunlight exposure. Second, because hepatitis and osteoporosis patients do not always consult with a clinic, these patients may

have been missed. Some participants with mild symptoms may also have been excluded. Finally, due to the observational study design, the determining definitive causality was limited. Further long-term intervention studies should be performed.

Conclusion

We suggest that the risk of osteoporosis might be higher in patients with hepatitis B, especially in females.

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Compliance with ethical standards

The Ethics Committee of Hallym University (2014-I148) approved the use of the data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The Institutional Review Board waived the requirement for written informed consent.

Conflicts of interest None.

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