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Risk of Hip Fracture Associated With Hepatitis C Virus Infection and Hepatitis C/Human Immunodeficiency Virus Coinfection

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Hepatitis C virus (HCV) infection has been associated with reduced bone mineral density, but its association with fracture rates is unknown, particularly in the setting of human immunodeficiency virus (HIV) coinfection. Our aims were to determine whether persons with HCV infection alone are at increased risk for hip fracture, compared to uninfected individuals, and to examine whether the risk of hip fracture is higher among HCV/HIV-coinfected persons, compared to those with HCV alone, those with HIV alone, and those uninfected with either virus. We conducted a cohort study in 36,950 HCV/HIV-coinfected, 276,901 HCV-monoinfected, 95,827 HIV-monoinfected, and 3,110,904 HCV/HIV-uninfected persons within the U.S. Medicaid populations of California, Florida, New York, Ohio, and Pennsylvania (1999-2005). Incidence rates of hip fracture were lowest among uninfected persons (1.29 events/1,000 person-years), increased with the presence of either HIV infection (1.95 events/1,000 person-years) or HCV infection (2.69 events/1,000 person-years), and were highest among HCV/HIV-coinfected individuals (3.06 events/1,000 person-years). HCV/HIV coinfection was associated with an increased relative hazard (adjusted hazard ratio [HR] [95% confidence interval; CI]) of hip fracture, compared to HCV-monoinfected (HR, 1.38; 95% CI: 1.25-1.53), HIV-monoinfected (females: HR, 1.76; 95% CI: 1.44-2.16; males: HR, 1.36; 95% CI: 1.20-1.55), and HCV/HIV-uninfected persons (females: HR, 2.65; 95% CI: 2.21-3.17; males: HR, 2.20; 95% CI: 1.97-2.47). HCV monoinfection was associated with an increased risk of hip fracture, compared to uninfected individuals, and the relative increase was highest in the youngest age groups (females, 18-39 years: HR, 3.56; 95% CI: 2.93-4.32; males, 18-39 years: HR, 2.40; 95% CI: 2.02-2.84). *Conclusion:* Among Medicaid enrollees, HCV/HIV coinfection was associated with increased rates of hip fracture, compared to HCV-monoinfected, HIV-monoinfected, and HCV/HIV-uninfected persons. HCV-monoinfected patients had an increased risk of hip fracture, compared to uninfected individuals. (HEPATOLOGY 2012;56:1688-1698)

Hepatitis C virus (HCV) infection exerts its main effects on the liver, inducing inflammation that leads to progressive liver fibrosis and, ultimately, cirrhosis in approximately 20% of chronic infections.[1] However, HCV infection can also affect organ systems outside of the liver,[2] particularly the skeletal system (termed "hepatic osteodystrophy"). Cross-sectional studies have shown that HCV infection is associated with reduced bone mineral density (BMD).[3-7] The mechanisms for HCV-induced

Abbreviations: BMD, bone mineral density; CI, confidence interval; CKD, chronic kidney disease; CMS, Centers for Medicare and Medicaid Services; DM, diabetes mellitus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; IGF-1, insulin-like growth factor 1; IL, interleukin; PPIs, proton pump inhibitors; TNF-α, tumor necrosis factor alpha.

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reductions in BMD remain unclear, but chronic inflammation and liver dysfunction in the setting of HCV-associated hepatic decompensation might contribute to hepatic osteodystrophy.[4,8-10]

Although chronic HCV infection is associated with reduced BMD,[3-7] no longitudinal study has been performed to evaluate incidence rates of fracture. In addition, because low BMD is a recognized metabolic complication of human immunodeficiency virus (HIV) infection,[11] HCV/HIV coinfection,[6] and antiretroviral therapy,[12] HCV/HIV coinfection might increase fracture risk beyond that of HIV or chronic HCV alone. Evaluating the risk of fracture associated with HCV infection and HCV/HIV coinfection is important, because these conditions are prevalent worldwide and because fractures, particularly those at the hip, adversely affect survival, with an effect on mortality similar to that of cardiovascular disease.[13] Furthermore, hip fractures cause significant pain and disability and typically require an emergency department visit, hospitalization, surgery, and rehabilitation stay, resulting in substantial healthcare costs.

This study sought to determine whether the reduced BMD that has been reported to be associated with HCV infection and HCV/HIV coinfection translates into clinically important increases in fracture risk. We first evaluated the incidence of hip fracture among patients with HCV infection alone, compared to HCV- and HIV-uninfected persons. We hypothesized that the risk of hip fracture was higher among patients with HCV monoinfection, compared to uninfected individuals. We then examined hip fracture incidence among HCV/HIV-coinfected patients, compared to those with HCV alone, those with HIV alone, and those uninfected with either virus. Our rationale for evaluating these three comparisons was to allow a more complete understanding of the hip fracture risk associated with HCV/HIV coinfection. We hypothesized that dual infection further increased the fracture risk, compared to HCV-monoinfected, HIV-monoinfected, and HCV/HIV-uninfected individuals.

Patients and Methods

Study Design and Data Source. We performed a retrospective cohort study among HCV/HIV-coinfected, HCV-monoinfected, HIV-monoinfected, and HCV/HIV-uninfected persons within the Medicaid populations of California, Florida, New York, Ohio, and Pennsylvania from 1999 to 2005. The Medicaid program consists of state-run programs with joint federal and state funding for hospital, medical, and outpatient care and drug benefits for low-income and special-needs individuals.[14] The states included in this study were selected because they represent five of the largest Medicaid programs in the United States, comprising approximately 22 million active enrollees, or almost 40% of the U.S. Medicaid population.[15,16] Medicaid claims report demographic information, inpatient and outpatient medical diagnoses (recorded by using International Classification of Diseases, Ninth Revision, diagnosis codes), and medications dispensed. Death dates were ascertained using Centers for Medicare and Medicaid Services (CMS) data supplemented with mortality information from the Social Security Administration Death Master File. Because 17% of Medicaid beneficiaries are coenrolled in Medicare, we obtained Medicare data on dually eligible persons.[17] Previous analyses of the linked Medicaid and Medicare claims indicate that the data are of high quality.[18] The study was approved by the University of Pennsylvania Institutional Review Board, and a data-use agreement was obtained from the CMS.

Study Patients. Patients 18 years of age or older with diagnoses of HCV and/or HIV infections were identified using previously validated algorithms.[19-21] HCV-monoinfected patients were defined by (1) a diagnosis of HCV infection and (2) no diagnosis of HIV infection or prescriptions for antiretroviral medications. HCV/HIV-coinfected patients had (1) a diagnosis of HCV infection, (2) a diagnosis of HIV infection, and (3) claims for antiretroviral medications on two separate occasions. We included only antiretroviral-treated HCV/HIV patients because current management guidelines recommend antiretroviral therapy in all HCV/HIV-coinfected patients, regardless of CD4 T-lymphocyte count.[22] The overall number of antiretroviral-untreated HCV/HIV-coinfected patients was too small to permit evaluation. HIV-monoinfected patients had (1) a diagnosis of HIV infection, (2) antiretroviral claims on two occasions, and (3) no diagnosis of HCV infection. HCV/HIV-uninfected patients

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had no HCV or HIV diagnoses and no antiretroviral prescriptions.

Patients were excluded if they had (1) only one Medicaid claim (i.e., no follow-up), (2) a hip fracture diagnosed before start of follow-up (defined below), (3) diagnosis of hepatitis B virus infection (to isolate the effect of HCV infection), or (4) received standard or pegylated interferon (IFN) (because this therapy affects BMD[23]).

We matched each HCV-monoinfected and HCV/HIV-coinfected patient on age (within 1 year), sex, and state with up to 10 randomly selected uninfected persons. Matching on these variables reduced to workable proportions the number of uninfected individuals for data analysis while maintaining balance between cohorts on these variables. Ninety-two percent of HCV-monoinfected patients were matched with 10 uninfected patients (minimum number of matches: 6). Ninety-three percent of HCV/HIV-coinfected patients were matched with 10 uninfected patients (minimum number of matches: 7). We did not match HCV/HIV-coinfected patients with HCV-monoinfected and HIV-monoinfected patients because the sample sizes of the two monoinfected cohorts were substantially smaller than the cohort of HCV/HIV-uninfected persons, thus making statistical analysis feasible.

The 90 days preceding the start of follow-up represented the baseline period for all cohorts, during which baseline comorbidities and therapies were determined. Follow-up for HCV-monoinfected, HCV/HIV-coinfected, and HIV-monoinfected patients began on the date of their initial HIV and/or HCV diagnosis. However, if the first claim in the database was an HIV and/or HCV diagnosis, follow-up began 90 days after their initial diagnosis. Follow-up for uninfected persons began 90 days after their initial claim. Follow-up continued until a hip fracture, death, or last claim before December 31, 2005.

Main Study Outcome. The primary outcome was a diagnosis of fracture of the proximal femur (hip). Diagnoses of hip fracture (Appendix A) from CMS claims were found to be highly valid in a previous survey, with 94% of cases confirmed by medical records.[24]

Data Collection. Demographic data collected included age, sex, race, and state of residence. Diagnoses associated with osteoporosis or risk of falling (Table 1) were recorded before or at the start of follow-up. Hepatic decompensation was defined by a diagnosis of ascites, spontaneous bacterial peritonitis, and/or variceal hemorrhage.[25] We also examined use of medications that affect bone metabolism (Table 1). Patients were considered exposed to a medication if a drug claim was recorded within 90 days before the start of follow-up.

Statistical Analysis. The number of fractures and person-time of observation was determined for each cohort. We estimated incidence rates (in events/1,000 person-years) and 95% confidence intervals (CIs) of hip fractures for each cohort using direct standardization by age, sex, and state to the characteristics of uninfected persons.[26]

The primary analysis examined the time to fracture. Rates of incident fractures were compared among the following cohorts: (1) HCV monoinfected and uninfected; (2) HCV/HIV coinfected and uninfected; (3) HCV/HIV coinfected and HIV monoinfected (to examine the effect of HCV infection on hip fracture risk in the setting of treated HIV infection); and (4) HCV/HIV coinfected and HCV monoinfected (to examine the effect of treated HIV on hip fracture risk in the setting of HCV infection). Major differences in the prevalence of medical comorbidities and baseline usage of medications associated with osteoporosis were observed between the cohorts (Table 1). Because of the many potential confounding variables relative to the number of hip fractures, we used propensity scores to balance, or control for, these confounders between the groups.[27,28] Separate propensity score models were developed using logistic regression for each of the four comparisons of interest (HCV monoinfected versus uninfected; HCV/HIV coinfected versus uninfected; HCV/HIV coinfected versus HIV monoinfected; and HCV/HIV coinfected versus HCV monoinfected). All variables listed in Table 1 were included in propensity score models, except for age, sex, and state (which were included as covariates in final multivariable models) and hepatic decompensation (because this condition might be in the causal pathway to fracture). Cox's proportional hazards analyses yielded hazard ratios (HRs) and 95% CIs of hip fracture, stratified by quintiles of propensity score and state.[29] We examined interactions between cohort, sex, and age groups (18-39, 40-49, 50-59, 60-69, and $\geq$70 years).

We next estimated cumulative incidences of hip fracture over the maximum period of observation (6.75 years) among HCV-monoinfected and HCV/HIV-coinfected patients, compared to uninfected patients, matched to have characteristics similar to each of the HCV-infected cohorts using Cox's propensity-score–weighted regression models.[30] Details appear in Appendix B.

Because cross-sectional studies suggest that HCV-infected patients with hepatic decompensation have

Table 1. Baseline Characteristics of Study Patients by Cohort

Characteristic	HCV/HIV Coinfected (n = 36,950)	HCV Monoinfected (n = 276,901)	HIV Monoinfected (n = 95,827)	HCV/HIV Uninfected Matched to HCV/HIV Coinfected Cohort* (n = 366,829)	HCV/HIV Uninfected Matched to HCV Monoinfected Cohort† (n = 2,744,075)
Median age, years (IQR)	42 (37-48)	47 (40-56)	39 (33-46)	42 (37-48)	48 (40-56)
Female sex, no. (%)	10,820 (29.3)	128,453 (46.4)	35,313 (36.9)	107,607 (29.3)	1,275,098 (46.5)
Race/ethnicity, no. (%)					
White	10,266 (27.8)	127,626 (46.1)	26,146 (27.3)	141,100 (38.5)	1,110,107 (40.5)
Black	14,700 (39.8)	58,868 (21.3)	42,554 (44.4)	72,017 (19.6)	456,909 (16.7)
Hispanic	2,939 (8.0)	38,950 (14.1)	8,100 (8.5)	61,606 (16.8)	476,099 (17.4)
Other	9,045 (24.5)	51,457 (18.6)	19,027 (19.9)	92,106 (25.1)	700,960 (25.5)
State, no. (%)					
California	7,872 (21.3)	117,495 (42.4)	21,901 (22.9)	78,213 (21.3)	1,165,817 (42.5)
Florida	6,261 (16.9)	32,549 (11.8)	25,688 (26.8)	62,073 (16.9)	320,888 (11.7)
New York	20,306 (55.0)	86,487 (31.2)	40,609 (42.4)	201,584 (55.0)	857,488 (31.2)
Ohio	1,003 (2.7)	20,673 (7.5)	4,066 (4.2)	9,957 (2.7)	204,459 (7.5)
Pennsylvania	1,508 (4.1)	19,697 (7.1)	3,563 (3.7)	15,002 (4.1)	195,423 (7.1)
Incident hip fractures, no. (%)	643 (1.7)	3,943 (1.4)	795 (0.8)	1,653 (0.5)	31,352 (1.1)
Median follow-up, years (IQR)	5.2 (2.9-6.7)	2.3 (0.9-4.2)	3.7 (1.6-6.4)	2.2 (0.7-5.3)	2.7 (0.9-6.0)
Total follow-up time, person-years	171,217	737,759	358,898	1,068,634	8,849,719
Baseline health condition, no. (%)‡					
Alcoholism	3,747 (10.1)	32,076 (11.6)	4,414 (4.6)	16,350 (4.5)	72,476 (2.6)
Asthma or COPD	3,254 (8.8)	34,915 (12.6)	6,462 (6.7)	16,846 (4.6)	173,662 (6.3)
Cancer	1,106 (3.0)	12,575 (4.5)	3,619 (3.8)	6,755 (1.8)	82,448 (3.0)
CKD	2,081 (5.6)	30,903 (11.2)	4,187 (4.4)	9,214 (2.5)	87,679 (3.2)
Dementia	609 (1.6)	6,032 (2.2)	1,390 (1.5)	1,962 (0.5)	35,791 (1.3)
DM	2,007 (5.4)	46,350 (16.7)	3,997 (4.2)	23,840 (6.5)	260,727 (9.5)
Congestive heart failure	804 (2.2)	18,577 (6.7)	1,795 (1.9)	6,257 (1.7)	88,884 (3.2)
Hepatic decompensation	366 (1.0)	12,176 (4.4)	483 (0.5)	1,195 (0.3)	10,404 (0.4)
Myocardial infarction	875 (2.4)	22,418 (8.1)	1,963 (2.0)	12,124 (3.3)	154,313 (5.6)
Peptic ulcer disease	410 (1.1)	6,861 (2.5)	863 (0.9)	3,001 (0.8)	29,726 (1.1)
Peripheral vascular disease	346 (0.9)	9,068 (3.3)	635 (0.7)	2,904 (0.8)	50,622 (1.8)
Rheumatoid arthritis/nonspecific arthropathy	604 (1.6)	12,308 (4.4)	1,017 (1.1)	5,086 (1.4)	62,344 (2.3)
Seizure disorder	1,096 (3.0)	11,484 (4.1)	2,221 (2.3)	7,424 (2.0)	53,981 (2.0)
Stroke	599 (1.6)	10,695 (3.9)	1,499 (1.6)	5,306 (1.4)	78,788 (2.9)
Baseline medication use, no. (%)§					
Anxiolytic	4,050 (11.0)	33,220 (12.0)	7,346 (7.7)	15,970 (4.4)	129,691 (4.7)
Antidepressant	9,801 (26.5)	71,173 (25.7)	18,734 (19.5)	33,672 (9.2)	275421 (10.0)
Anticonvulsant/gabapentin	4,697 (12.7)	42,979 (15.5)	9,790 (10.2)	21,762 (5.9)	165,637 (6.0)
Antiparkinsonian	532 (1.4)	7,278 (2.6)	1,115 (1.2)	6,479 (1.8)	46,878 (1.7)
Antipsychotic	3,344 (9.1)	33,558 (12.1)	7,212 (7.5)	20,707 (5.6)	143,678 (5.2)
Calcium supplementation	433 (1.2)	6,009 (2.2)	738 (0.8)	1,683 (0.5)	26,383 (1.0)
Corticosteroid (inhaled)	1,208 (3.3)	11,148 (4.0)	2,473 (2.6)	5,713 (1.6)	49,886 (1.8)
Corticosteroids (oral)	1,208 (3.3)	10,810 (3.9)	3,641 (3.8)	6,740 (1.8)	59,219 (2.2)
Hormone therapy (estrogen)	594 (1.6)	8,335 (3.0)	1,220 (1.3)	2,864 (0.8)	57,296 (2.1)
NSAID/aspirin	6,442 (17.4)	39,704 (14.3)	13,264 (13.8)	34,920 (9.5)	270,594 (9.9)
PPI	2,991 (8.1)	40,131 (14.5)	6,906 (7.2)	14,791 (4.0)	126,757 (4.6)
Statin	545 (1.5)	15,003 (5.4)	2,495 (2.6)	13,013 (3.5)	140,876 (5.1)
Tenofovir	599 (1.6)	18 (0.0)	3,538 (3.7)	0 (0.0)	0 (0.0)
Testosterone	909 (2.5)	600 (0.2)	2,707 (2.8)	268 (0.1)	2,371 (0.1)
Thiazide diuretic	868 (2.3)	17,730 (6.4)	2,030 (2.1)	9,492 (2.6)	103,024 (3.8)
Thyroxine	320 (0.9)	9,543 (3.4)	813 (0.8)	4,633 (1.3)	56,915 (2.1)

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug.

*Up to 10 HCV/HIV-uninfected patients were matched on age, sex, and state with each HCV/HIV-coinfected subject.

†Up to 10 HCV/HIV-uninfected patients were matched on age, sex, and state with each HCV-monoinfected subject.

‡Cohorts were also evaluated for celiac disease, Cushing's disease, hyperparathyroidism, inflammatory bowel disease, obesity, osteomalacia, Paget's disease, and systemic lupus erythematosus, but the prevalence was <2% within each group. Please see Appendix C for the prevalence of these additional health conditions in each cohort.

§Cohorts were also evaluated for use of bisphosphonates, calcitonin, cholestyramine, and vitamin D, but the prevalence of use of these medications was <2% within each group. Please see Appendix C for the prevalence of use of these medications in each cohort.

lower BMD than HCV-infected persons with healthy liver function,[3,4] we conducted an exploratory analysis to evaluate whether HCV-monoinfected patients with hepatic decompensation had an increased risk of hip fracture, compared to similar monoinfected patients without this diagnosis. Propensity score models

estimated the probability of decompensation. Each HCV-monoinfected patient with hepatic decompensation was matched 1:1 on propensity score (nearest-neighbor matching within 0.02 of the propensity score), sex, and state to a monoinfected patient without decompensation.[31] Cox's models evaluated relative hazards of fracture associated with hepatic decompensation.

Finally, given that HCV/HIV-coinfected patients may have had their HCV and HIV diagnoses recorded on different dates and because the earlier diagnosis date represented the start of follow-up, we conducted sensitivity analyses to evaluate HRs of fractures using the later date of these patients' diagnoses as the start of follow-up. We also conducted a sensitivity analysis to examine the effect of potentially unmeasured confounders on the relative hazard of hip fracture.[32]

We estimated that 5,632 HCV-infected patients would provide 90% power to detect a relative hazard of hip fracture of 1.5 between HCV-infected and -uninfected persons, assuming a two-tailed alpha of 0.05 and a 1% rate of fracture among the uninfected cohort.[33] Data were analyzed using SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics. Among 42,507,874 patients enrolled in the five states between 1999 and 2005 (Fig. 1), we identified 301,132 (0.7%) HCV-monoinfected, 38,661 (0.09%) HCV/HIV-coinfected, and 96,991 (0.2%) HIV-monoinfected individuals. We matched 3,007,974 HCV/HIV-uninfected persons on age, sex, and state to the HCV-monoinfected cohort and similarly matched 386,610 uninfected individuals to the coinfected cohort. After exclusions (Fig. 1), the final sample included 276,901 HCV-monoinfected, 36,950 HCV/HIV-coinfected, 95,827 HIV-monoinfected, and 2,744,075 uninfected patients matched to the HCV-monoinfected cohort and 366,829 uninfected patients matched to the coinfected cohort.

Table 1 summarizes the demographic and clinical characteristics of the infected cohorts and the characteristics of age-, sex-, and state-matched uninfected patients. HCV-monoinfected patients were older, more frequently female, and more commonly of white race than HCV/HIV-coinfected and HIV-monoinfected patients. In addition, compared to coinfected and HIV-monoinfected patients, HCV-monoinfected patients more commonly had medical diagnoses that had known associations with osteoporosis or risk of falling, including alcoholism, asthma, cardiovascular disease, diabetes mellitus (DM), chronic kidney disease (CKD), hyperparathyroidism, and rheumatoid arthritis. HCV-monoinfected patients also more frequently received medications associated with osteoporosis, particularly corticosteroids and proton pump inhibitors (PPIs).

Unadjusted Incidence Rates of Hip Fracture. Median follow-up time ranged from 2.3 years for HCV-monoinfected patients to 5.2 years for HCV/HIV-coinfected patients (Table 1). Unadjusted incidence rates of hip fractures were lowest among uninfected persons (HR: 1.29 [95% CI: 0.85-1.94] events/1,000 person-years), increased with the presence of either HIV (HR: 1.95 [95% CI: 1.33-2.85] events/1,000 person-years) or HCV infection (HR: 2.69 [95% CI: 1.96-3.70] events/1,000 person-years), and were highest among HCV/HIV-coinfected patients (HR: 3.06 [95% CI: 1.96-4.80] events/1,000 person-years).

Risk of Hip Fracture in HCV-Monoinfected Patients, Compared to Uninfected Persons. After adjusting for age, sex, state, propensity score, and interaction between sex and age, HCV monoinfection was associated with an increased rate of hip fracture, compared to uninfected persons (adjusted HR, 1.47; 95% CI: 1.42-1.52). However, relative hazards of hip fractures associated with HCV monoinfection varied by sex and age groups ($P < 0.001$ for all interactions). Below the age of 70 years, HCV infection was associated with an increased relative hazard of hip fracture, compared to uninfected individuals, regardless of sex (Table 2). For both women and men, HRs were highest for persons 18-39 years and lowest for those 60-69 years. Among persons 70 years and older, no association between HCV infection and hip fracture was observed. Relative hazards of hip fracture were higher for women than men among those below 50 years.

Cumulative incidences of hip fractures for HCV-monoinfected and -uninfected persons, grouped by sex and age, are shown in Table 2. Among women, HCV monoinfection was associated with 6.2 additional hip fractures per 1,000 for the youngest age group (18-39 years) and 15.9 additional hip fractures per 1,000 for the oldest group (≥70 years). Among men, HCV monoinfection resulted in an estimated 7.8 additional hip fractures per 1,000 for the youngest age group (18-39 years) and 19.3 additional fractures per 1,000 for the oldest group (≥70 years).

Among HCV-monoinfected patients, hepatic decompensation was associated with an increased rate of hip fractures (HR, 1.22; 95% CI: 1.02-1.46).

Risk of Hip Fracture in HCV/HIV-Coinfected Patients, Compared to Uninfected Persons. HRs of hip fractures associated with HCV/HIV coinfection varied by sex in comparisons with uninfected persons

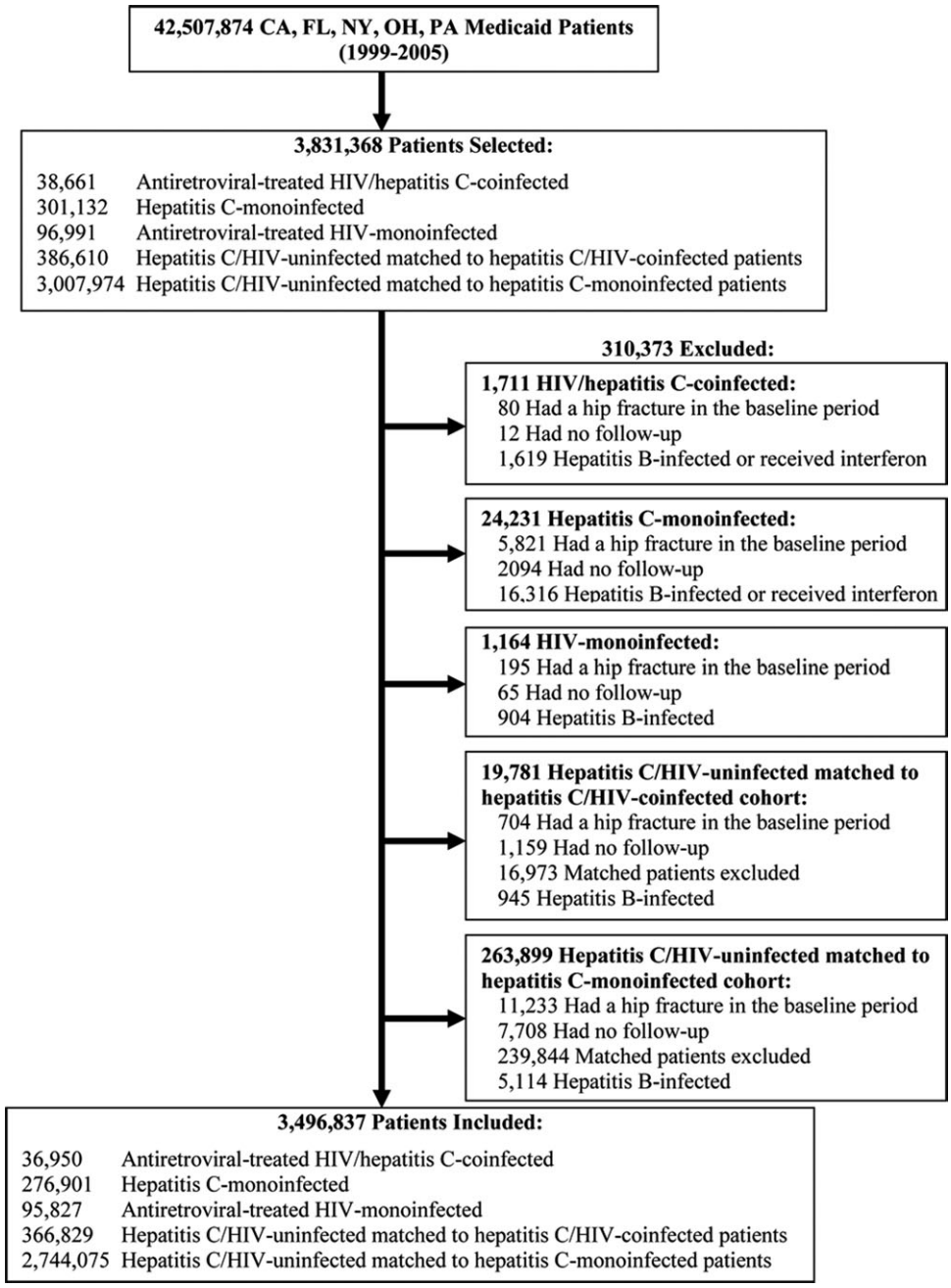

Fig. 1. Selection of HCV/HIV-coinfected, HCV-monoinfected, HIV-monoinfected, and HCV/HIV-uninfected patients in the study.

($P < 0.001$ for interaction), but not by age group. Antiretroviral-treated HCV/HIV-coinfected patients had higher rates of hip fracture, compared to persons uninfected with either virus (Table 3). HRs for fracture appeared higher among women than men. Similar results were observed when the later date of HCV or HIV diagnosis was used as the start of follow-up.

Cumulative incidences of hip fractures for HCV/HIV-coinfected and -uninfected persons, grouped by sex and age, are shown in Table 3. Among women, coinfection was associated with 4.9 additional hip fractures per 1,000 for the youngest age group (18-39 years) and 30.5 additional hip fractures per 1,000 for the oldest group (≥50 years). Among men, coinfection resulted in an estimated 9.1 additional hip fractures per 1,000 for the youngest age group (18-39 years) and 25.3 additional fractures per 1,000 for the oldest group (≥50 years).

Risk of Hip Fracture in HCV/HIV-Coinfected Compared to HCV-Monoinfected and HIV-Monoinfected Persons. Rates of hip fractures associated with HCV/HIV coinfection varied by sex in comparisons with HIV-monoinfected ($P < 0.001$ for interaction). Antiretroviral-treated HCV/HIV-coinfected patients had higher rates of hip fracture, compared to antiretroviral-treated HIV-monoinfected patients (females: HR,

Table 2. Estimated Hip Fracture Rates and Relative Hazards of Hip Fracture (With 95% CIs) for HCV-Monoinfected Patients, Compared to Those Uninfected With Either HIV or HCV Infections, by Sex and Age Group

Sex, Age Group (Years)	HCV Status	No. of Patients	Hip Fracture Rate Per 1,000	Additional Hip Fractures Per 1,000 HCV Patients	Adjusted HR of Hip Fracture (95% CI)*
Females					
18-39	HCV Infected	33,060	10.8	6.2	3.56 (2.93-4.32)
	Uninfected	330,161	4.6		Ref
40-49	HCV Infected	41,736	21.5	8.0	2.04 (1.83-2.28)
	Uninfected	409,461	13.5		Ref
50-59	HCV-Infected	25,575	39.1	12.0	1.56 (1.40-1.73)
	Uninfected	256,917	27.1		Ref
60-69	HCV-Infected	14,457	64.9	18.2	1.41 (1.27-1.57)
	Uninfected	144,787	46.7		Ref
≥70	HCV-Infected	13,625	128.2	15.9	0.96 (0.89-1.04)
	Uninfected	133,772	112.3		Ref
Males					
18-39	HCV-Infected	28,909	16.2	7.8	2.40 (2.02-2.84)
	Uninfected	284,389	8.3		Ref
40-49	HCV-Infected	55,462	26.2	10.6	1.93 (1.76-2.11)
	Uninfected	519,230	15.7		Ref
50-59	HCV-Infected	39,867	37.7	12.7	1.60 (1.46-1.76)
	Uninfected	417,434	24.9		Ref
60-69	HCV-Infected	15,231	60.8	25.1	1.70 (1.52-1.91)
	Uninfected	158,546	35.7		Ref
≥70	HCV-Infected	8,979	89.8	19.3	1.10 (0.98-1.24)
	Uninfected	89,378	70.6		Ref

*Final model included terms for cohort, age, sex, state, propensity score, and interactions between cohort and sex, cohort and age, age and sex, and age, sex, and cohort.

1.76 [95% CI: 1.44-2.16]; males: HR, 1.36 [95% CI: 1.20-1.55]).

HRs of hip fractures were not different by age and sex for comparisons between HCV/HIV-coinfected and HCV-monoinfected patients. HCV/HIV coinfection was associated with a higher rate of hip fracture, compared to HCV-monoinfected patients (adjusted HR, 1.38; 95% CI: 1.25-1.53).

Similar results were observed when the later date of HCV or HIV diagnosis was used as the start of follow-up.

Potential Effect of Unmeasured Confounders. Sensitivity analyses to evaluate the effect of unmeasured confounding determined that an unmeasured confounder would need to have >20% prevalence and be 3.5 times more likely to be present among HCV-

Table 3. Estimated Hip Fracture Rates and Relative Hazards of Hip Fracture (With 95% CIs) for Antiretroviral-Treated HIV/HCV-Coinfected Patients, Compared to Persons Uninfected With Either Virus, by Sex and Age Group

Sex, Age Group (Years)*	HCV Status	No. of Patients	Hip Fracture Rate Per 1,000	Additional Hip Fractures Per 1,000 HCV/HIV Patients	Adjusted Hazard Ratio of Hip Fracture (95% CI)†
Females					
18-39	HCV/HIV-Coinfected	4,310	8.9	4.9	2.77 (1.76-4.37)
	Uninfected	43,175	4.0		Ref
40-49	HCV/HIV-Coinfected	5,026	28.0	17.3	2.89 (2.26-3.71)
	Uninfected	49,491	10.7		Ref
≥50	HCV/HIV-Coinfected	1,484	52.1	30.5	2.27 (1.65-3.11)
	Uninfected	14,941	21.6		Ref
Males					
18-39	HCV/HIV-Coinfected	8,505	17.4	9.1	2.28 (1.80-2.89)
	Uninfected	84,386	8.3		Ref
40-49	HCV/HIV-Coinfected	12,619	28.3	14.3	2.27 (1.94-2.67)
	Uninfected	124,650	14.0		Ref
≥50	HCV/HIV-Coinfected	5,006	47.6	25.3	2.06 (1.70-2.50)
	Uninfected	50,186	22.3		Ref

*Because of the small number of HCV/HIV-coinfected patients above the age of 60 years, we were unable to evaluate comparisons in the 60-69-year and ≥70-year strata and have limited evaluation to the ≥50-year age range.

†Final models for each comparison included terms for cohort, age, sex, state, propensity score, and interactions between cohort and sex, age, and sex.

uninfected than -infected persons to make the results nonsignificant.

Discussion

Among U.S. Medicaid enrollees, antiretroviral-treated HCV/HIV-coinfected patients experienced increased rates of hip fractures, compared to HCV-monoinfected, antiretroviral-treated HIV-monoinfected, and HCV/HIV-uninfected persons. HCV monoinfection was associated with an increased rate of hip fractures, compared to uninfected persons below age 70, and the relative increase was highest among younger persons. Additionally, HCV-monoinfected patients with hepatic decompensation had higher rates of hip fractures, compared to those without decompensation. Finally, HRs of hip fractures were higher among women than men.

The mechanisms for the association between HCV infection and hip fracture remain unclear. Elevated serum levels of inflammatory cytokines associated with chronic HCV infection (e.g., tumor necrosis factor-alpha [TNF-α], interleukin [IL]-1, and IL-6) could increase receptor activator of nuclear factor kappa B ligand, promoting osteoclastogenesis and increasing bone resorption.[4,8] Moreover, TNF-α inhibits osteoblast differentiation, inhibits collagen synthesis in osteoblasts, and promotes osteoblast apoptosis.[8] The net effect of this inflammatory cascade is reduced BMD and increased fracture risk. Furthermore, compensated cirrhosis and liver synthetic dysfunction in the setting of hepatic decompensation could increase the risk of hypogonadism,[10] reduce hepatic hydroxylation of vitamin D,[9] and impair hepatic production of insulin-like growth factor 1 (IGF-1), which promotes bone formation,[7] and these conditions could further reduce bone density and contribute to fractures. Our finding that hepatic decompensation was associated with increased rates of hip fractures suggests that liver dysfunction might also contribute to metabolic bone disease.[3,4] Finally, illicit drug use, alcohol abuse, poor nutrition, and fragility among HCV-infected patients might also contribute to increased fracture risk from trauma, irrespective of the effect of HCV infection on BMD. Additional research is needed to determine the mechanisms by which chronic HCV and HCV/HIV coinfection affect BMD and fracture incidence.

The higher fracture rates observed among HCV/HIV-coinfected persons, compared to HCV-monoinfected individuals, might be the result of the additive effects of HIV infection and antiretroviral therapy on BMD. Uncontrolled HIV viremia up-regulates cytokines that reduce osteoblast activity, promote osteoblast apoptosis, and activate osteoclasts to increase bone resorption.[34,35] HIV infection might increase the risk of other osteoporosis risk factors, such as poor nutrition, hypogonadism, lipoatrophy, and decreased muscle mass.[36,37] Moreover, initiation of antiretroviral therapy is associated with significant short-term bone loss in the range of 2%-6% over 1-2 years.[38] In particular, tenofovir use has been linked to decreased BMD among HIV-infected adults,[39] possibly because of phosphate wasting from tenofovir-induced proximal renal tubule dysfunction.[40]

Comparisons between HCV-monoinfected and -uninfected individuals demonstrated that HRs were highest among younger persons and decreased with higher age. In terms of absolute differences, however, the increase was highest for older patients because of high absolute fracture rates in this group. These results are to be expected because many other factors contribute to fracture risk with advancing age and likely overwhelm the effect of HCV infection. The mechanism for the increased relative hazards of hip fracture at the younger ages remains unclear. Although this finding could reflect the role of chronic HCV-associated inflammation, it also suggests that trauma might be contributing to fractures among younger patients. The data did not permit determination of fractures associated with trauma.

We observed that the relative hazards of hip fracture were higher for women than men, when comparing HCV-monoinfected and -uninfected persons below age 50, HCV/HIV-coinfected and HIV-monoinfected patients, and coinfected and uninfected persons. The pathogenesis responsible for these differences is unclear. It is unknown whether there are clinically significant differences by sex in serum levels of hepatitis-associated cytokines, markers of bone turnover, or other factors that maintain bone balance (e.g., IGF-1) among HCV-infected patients. Moreover, the effect of HCV infection, particularly in the setting of hepatic decompensation, on ovarian function and estrogen production in women is also unknown. Future studies of serum levels of cytokines, markers of bone turnover, IGF-1, and sex hormones might elucidate the mechanisms for low bone density and fracture in HCV-infected women.

Although higher rates of fracture associated with HCV monoinfection and HCV/HIV coinfection have potential implications for clinical management, neither of these conditions is considered to be associated with increased fracture risk by osteoporosis guidelines.[41] Our study suggests that HCV monoinfection and

HCV/HIV coinfection are associated with an increased risk of fracture. Future studies are needed to determine the relations between dual-energy X-ray absorptiometry estimates of BMD and fracture risks associated with HCV monoinfection and HCV/HIV coinfection, and to develop guidelines for the identification of patients at risk. Determination of the mechanisms of reduced BMD resulting from HCV and HCV/HIV coinfection is also needed to identify potential interventions that might prevent bone loss and mitigate fracture risk in these populations.

Our study had several limitations. We lacked laboratory data on HCV and HIV infections as well as radiographic confirmation of fracture diagnoses. However, diagnoses of HCV and HIV infections were identified using previously validated algorithms.[19-21] Furthermore, hip fracture diagnoses in Medicaid were shown to have 94% positive predictive value.[24]

Second, we observed major differences in the prevalence of medical comorbidities and usage of medications associated with osteoporosis between cohorts. However, we addressed this by developing separate propensity score models for each of the four comparisons of interest to balance, or control for, potential confounding variables across comparison groups.

Third, our analyses only accounted for baseline use of antiviral treatment for chronic HCV infection, tenofovir use, and pharmacologic therapies for osteoporosis. We did not censor follow-up at the time of receipt of these medications, because use of these drugs was uncommon among the cohorts studied and because it is unclear whether hip fracture risk is affected by some of these therapies (i.e., tenofovir, IFN, and ribavirin).

Fourth, the median follow-up among the HCV/HIV-coinfected cohort was longer than that for the age-, sex-, and state-matched HCV/HIV-uninfected cohort. If our study design had called for two cohorts followed over time from the same starting age, this longer observation time would have limited possible comparisons. However, both coinfected and uninfected cohorts included patients among all age groups, produced risk sets of adequate size for all combinations of hip fracture risk factors across age groups, and therefore covered the spectrum of risks experienced by young, middle-aged, and older patients.

Fifth, residual confounding by unmeasured factors is possible in observational studies. We did not have information on body mass index, smoking, alcohol, illicit drug use, and duration of HCV and HIV infections. We also could not assess whether fractures were specifically trauma related. However, to negate the positive associations observed in our study, such confounders would have to be strongly associated with fracture and related to infection, but not related to the many risk factors already included in our models.

Finally, the study sample consisted of U.S. Medicaid enrollees, potentially limiting the generalizability of our results. However, Medicaid is the largest source of care for patients with HIV infection in the United States and provides coverage to a large proportion of patients with HCV infection.[42] In addition, the study cohorts are demographically similar to U.S. HCV and HIV populations.[43,44]

Our study had a number of strengths. It evaluated the association between HCV infection and hip fracture, including among HIV-infected persons, in a large population. The study also examined the risk of hip fracture associated with HCV-induced hepatic decompensation. Furthermore, propensity score methods enabled us to adjust for many potential confounding variables that have not been considered in previous fracture studies.

In conclusion, this study provides evidence that HCV and HCV/HIV coinfection are associated with increased rates of hip fractures. Future studies should evaluate mechanisms for the increased fracture risks in these populations.

Acknowledgment: Results withstood CMS privacy review and were approved for publication.

Appendix A

International Classification of Diseases, Ninth Revision (ICD-9), Codes for Hip Fracture

ICD-9 Diagnostic Code	Code Description
820.0	Transcervical fracture of femur neck, closed
820.1	Transcervical fracture of femur neck, open
820.2	Pertrochanteric fracture of femur neck, closed
820.3	Pertrochanteric fracture of femur neck, open

Appendix B

Estimation of Cumulative Incidence of Hip Fractures. We estimated the cumulative incidence of hip fracture estimated at the maximum period of observation (i.e., 6.75 years) separately among HCV-monoinfected and HCV/HIV-coinfected patients, compared to uninfected persons, standardized by weighting the uninfected individuals to have the characteristics of the infected and implementing weighted proportional hazards regressions.[34] First, we estimated the predicted probability of HCV infection for each person using logistic regression for each combination of age, sex, and state, with diagnoses and medications as predictors. We calculated weights equal to 1.0 for infected patients and predicted odds of infection for all uninfected persons, then grouped patients into deciles of calculated weights. We stabilized

individual weights by assigning to each uninfected person the median weight of the decile into which that person fell. This adjustment trimmed the weights of persons with extremely high (close to 1.0) or low (close to 0.0) predicted probabilities of HCV infection and dampened instabilities caused by these extremes.[34] When applied in regression models evaluating fractures, this method of weighting of HCV-infected and -uninfected persons standardizes comparisons to the characteristics of infected persons. We then performed 10 separate Cox's weighted regression models for each combination of sex and age group, with HCV infection as the only covariate, to estimate hip fracture rates among infected and uninfected persons.[48]

Appendix C

Additional Baseline Characteristics of Study Patients Evaluated by Cohort

Characteristic	HCV/HIV Coinfected (n = 36,950)	HCV Monoinfected (n = 276,901)	HIV Monoinfected (n = 95,827)	HCV/HIV Uninfected Matched to HCV/HIV Coinfected Cohort* (n = 366,829)	HCV/HIV Uninfected Matched to HCV Monoinfected Cohort† (n = 2,744,075)
Baseline health condition, no. (%)					
Celiac disease	0 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)	14 (0.0)
Cushing's disease	3 (0.0)	73 (0.0)	4 (0.0)	37 (0.0)	359 (0.0)
Hyperparathyroidism	100 (0.3)	2,270 (0.8)	115 (0.1)	323 (0.1)	3,518 (0.1)
Inflammatory bowel disease	68 (0.2)	1,126 (0.4)	231 (0.2)	653 (0.2)	4,899 (0.2)
Obesity	24 (0.1)	1,585 (0.6)	89 (0.1)	909 (0.2)	7,587 (0.3)
Osteomalacia	147 (0.4)	2,910 (1.1)	179 (0.2)	313 (0.1)	3,182 (0.1)
Paget's disease	2 (0.0)	53 (0.0)	4 (0.0)	16 (0.0)	286 (0.0)
Systemic lupus erythematosus	32 (0.1)	1,215 (0.4)	88 (0.1)	450 (0.1)	4,131 (0.2)
Baseline medication use, no. (%)					
Bisphosphonate	24 (0.1)	3,369 (1.2)	105 (0.1)	533 (0.1)	12,704 (0.5)
Calcitonin	9 (0.0)	741 (0.3)	26 (0.0)	131 (0.0)	4,274 (0.2)
Cholestyramine	47 (0.1)	554 (0.2)	82 (0.1)	171 (0.0)	1,580 (0.1)
Vitamin D	83 (0.2)	1,319 (0.5)	124 (0.1)	288 (0.1)	2,857 (0.1)

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug.
*Up to 10 HCV/HIV-uninfected patients were matched on age, sex, and state with each HCV/HIV-coinfected subject.
†Up to 10 HCV/HIV-uninfected patients were matched on age, sex, and state with each HCV-monoinfected subject.

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