Impact of Systemic Lupus Erythematosus on the Risk of Newly Diagnosed Hip Fracture: A General Population-Based Study

Lingyi Li,¹ Hui Xie,² Na Lu,¹ John M. Esdaile,³ and J. Antonio Aviña-Zubieta³

Objective. Hip fractures have serious consequences, including a 1-year mortality rate of 30%. Population-based studies on hip fractures in individuals with systemic lupus erythematosus (SLE) are scarce. Our objective was to assess the independent risk of hip fractures in patients with newly diagnosed SLE compared to the general population, accounting for baseline and time-varying confounders.

Methods. A cohort of all patients with incident SLE who received health care between January 1, 1997 and March 31, 2015 was assembled. The primary outcome was the occurrence of the first hip fracture since the study entry date. Individuals without SLE were randomly selected from the general population and matched (5:1) to those with SLE based on age, sex, and index year. Cumulative incidence was calculated after accounting for competing risks of death. Marginal structural Cox models were used to estimate the impact of SLE on hip fractures, adjusting for baseline and time-dependent covariates (i.e., glucocorticoid use and the number of outpatient, inpatient, and rheumatologist visits).

Results. Among 5,047 individuals with incident SLE and 25,235 individuals without SLE (86% female, mean age 40 years), we found 73 and 272 hip fractures during 78,915 and 395,427 person-years, respectively. The crude incidence rate ratio was 1.34 (95% confidence interval [95% CI] 1.02–1.75). After adjusting for baseline covariates, the hazard ratio (HR) was 1.86 (95% CI 1.37–2.52). After further adjustment for time-dependent covariates, the HR remained significant at 1.62 (95% CI 1.06–2.48).

Conclusion. Patients with newly diagnosed SLE have a 62% increased risk of hip fractures compared to individuals without SLE. For patients with SLE, this result has important implications for prevention of osteoporosis, which may lead to hip fractures.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune inflammatory disease with extensive morbidity and premature mortality (1). A recent study suggests that survival rates of patients with SLE have not improved in recent years (2); therefore, the emphasis on prevention of complications that contribute to permanent organ damage and increased mortality among patients with SLE is critical.

Osteoporosis and osteoporotic fractures contribute to damage in one of the most frequently involved organ systems in SLE, the musculoskeletal system (3). The etiology likely involves nondisease-related (e.g., glucocorticoid-induced adverse effects) as well as disease-related factors (e.g., inflammation due to disease activity) that contribute to bone loss in SLE (3,4). Previous studies have shown that patients with SLE have an increased risk of osteoporosis and fractures (3). Hip fractures represent the most devastating complication of osteoporosis, with up to 30% 1-year mortality and 60% 5-year mortality (5,6). However, studies on whether SLE is an independent risk factor for hip fractures (regardless of glucocorticoid use) are scarce and inconclusive, especially population-based studies (7,8).

All inferences, opinions, and conclusions drawn in this article are those of the authors and do not reflect the opinions or policies of the Data Stewards.

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

• The 62% increased risk of hip fractures in patients with newly diagnosed systemic lupus erythematosus (SLE) is independent of traditional risk factors, including glucocorticoid use. This finding provides evidence on the direct role of SLE in the risk of hip fractures.
• SLE and its chronic inflammation should be considered new risk factors for hip fractures.
• Our results call for an increased awareness of and improved strategy to prevent hip fractures in patients with SLE.

A case–control study, a cross-sectional study, and a meta-analysis showed a significant association between SLE and hip fractures, with the risk ranging from 1.99 to 5.10 (4,9,10). Furthermore, 1 cohort study that used electronic medical records from primary care physicians in the UK showed an increased risk of hip fractures among patients with rheumatoid arthritis or SLE, with hazard ratios (HRs) ranging from 1.69 to 1.90 (11). However, that study did not test the association between SLE and hip fractures alone. Another matched cohort study from Taiwan reported a crude incidence rate ratio of 2.23 (95% confidence interval [95% CI] 1.51–3.32) for the risk of hip fractures in the SLE cohort compared to the general population but did not adjust for baseline or time-dependent risk factors (7). A more recent cohort study using Medicaid data from the US with a shorter follow-up time (2007–2010) reported an HR of 3.22 (95% CI 2.33–4.46) (12). In contrast, a substantially smaller and statistically insignificant HR of 1.09 (95% CI 0.65–1.82) was reported in the UK, after adjusting for baseline and time-dependent risk factors using the time-dependent Cox proportional hazards model (8). Existing literature on longitudinal observation data analysis has shown the importance of accounting for time-dependent confounders or mediators via inverse weighting rather than adding them as covariates as in traditional Cox proportional hazards models (13,14). Covariates like glucocorticoids play an important role in the treatment of SLE and can cause glucocorticoid-induced osteoporosis (15); therefore, analysis needs to isolate and account for variables that can be intermediary variables between SLE and hip fracture.

The 4 cohort studies mentioned above used prevalent SLE cohorts, which have an inherent survival bias because the cohorts only included survivors, who may be less susceptible to hip fractures (16). Thus, despite the potentially important association between SLE and hip fractures, the current literature is inconclusive about the role of SLE-associated chronic inflammation on the risk of hip fractures, and findings are conflicting due to inadequacies in the design and analytical approaches, as mentioned above.

The aim of this study was both to estimate the overall risk of hip fractures in an incident SLE cohort compared to the general population and to estimate the independent effect of SLE on the occurrence of hip fractures after adjusting for nondisease-related factors (e.g., medication-induced adverse effects, particularly from glucocorticoid use) and other traditional hip fracture risk factors at baseline and during follow-up.

SUBJECTS AND METHODS

Universal health care coverage is available for all residents of the province of British Columbia (BC), Canada (population ~4.7 million). Population Data BC encompasses all provincially funded health care service data from January 1, 1990 to March 31, 2015, including all health care professional visits (17), hospitalizations (18), registration on the provincial medical services plan (19), cancer registry (20), and vital statistics (21). Furthermore, Population Data BC includes the comprehensive prescription drug database PharmaNet (22), which captures all dispensed medications in outpatient settings for all BC residents since 1996. Several population-based studies have been successfully conducted using Population Data BC (23–25).

Study design and cohort definitions. Using Population Data BC, a 1:5 matched cohort study on the risk of incident hip fractures among patients with incident SLE (SLE cohort) compared with age-, sex-, and index year–matched individuals who were randomly selected from the general population (non-SLE cohort) was conducted.

SLE cohort. The case definition of incident SLE included: 1) individuals age ≥18 years; 2) 2 principal International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM 710.0) or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification (ICD-10-CM M32.1, M32.8, M32.9) codes for SLE at least 2 months apart within 2 years from any type of physician or hospital visit; and 3) no SLE diagnosis in a 7-year run-in period prior to the first ICD code for SLE. The date of the second diagnosis date made within the timeframe (i.e., earliest time on the database after meeting the SLE case definition) was defined as the SLE index date. Of the patients with SLE, 99.4% were diagnosed by rheumatologists or from hospitalization. Similar case definitions using Swedish registry data have been validated, with a sensitivity of 97.6% and a positive predictive value of 97.5% (26).

Non-SLE cohort. To assemble the comparison cohort, data for a random sample of ~2 million BC residents registered with the provincial medical services plan during the study period were used. Individuals without any history of SLE diagnosis were selected and matched to patients with SLE (5:1) based on age, sex, and calendar year of the SLE index date. Patients with SLE were also eligible to be selected into the non-SLE cohort prior to their diagnosis. To be comparable with the SLE cohort, all individuals in the non-SLE cohort had a 7-year run-in period, the same criterion applied to the SLE cohort.
Exposure assessment. The primary exposure in the primary analysis was the diagnosis of SLE as defined above, which is a time-varying variable that changes its value from no to yes at the time of SLE diagnosis. The study period spanned from the study entry date (i.e., 7 years after the first registration date on the medical services plan) for each individual to March 31, 2015.

Ascertainment of hip fracture. The primary outcome was the occurrence of the first hip fracture since the study entry date. Incident hip fractures (ICD-9-CM codes 820.0, 820.2; ICD-10-CM codes S72.0, S72.1, S72.2) were identified using hospitalization data. Similar definitions for hip fractures have been used in previous publications and were found to have a positive predictive value of 63–96% in a general practitioner database (27). Individuals without a diagnosis of hip fractures, pathologic fractures, or Paget’s disease before the study entry date were selected into our study and were followed until they either experienced an outcome (i.e., hip fracture) or died or the follow-up period ended, whichever occurred first.

Covariate assessment. Baseline covariates were assessed within 12 months prior to the study entry date, including known potential risk factors for hip fractures. Covariates included age, sex, health resource utilization (number of outpatient visits, rheumatologist visits, hospitalizations), medication use (oral or injectable glucocorticoids [outpatient only], fibrates, statins, anti-diabetes medications, anticoagulant therapy, other cardiovascular drugs, antidepressant drugs, nonsteroidal anti-inflammatory drugs [NSAIDs], hormone replacement therapy [HRT], cyclooxygenase-2 [COX-2] inhibitors, and contraceptives), comorbidities (hypertension, cerebrovascular disease, alcoholism, ischemic heart disease, myocardial infarction, congestive heart failure, depression, malignancy, and chronic obstructive pulmonary disease [COPD]–related diseases). In addition, a history of surgery and the Romano modification of the Charlson Comorbidity Index for administrative data were also ascertainment (28). To estimate time-varying covariates, the follow-up time was divided into 19 time blocks (12 months per block) for each individual. Variables were then assessed in each 12-month period. These included glucocorticoid use (i.e., a binary variable) and health resource utilization (i.e., continuous variables), which acted as surrogates for disease activity.

Statistical analysis. Baseline characteristics of SLE and non-SLE cohorts were compared using chi-square tests for categorical variables or Wilcoxon’s rank sum tests for continuous variables. To calculate the risk of hip fractures during follow-up, the incidence rates per 1,000 person-years were calculated. Follow-up person-time from the study entry date until the date of hip fractures, death, or the date when the follow-up period ended, whichever occurred first, was computed. The Fine and Gray method was used to compare cumulative incidence functions that adjust for the competing risk of death (29).

A multivariable Cox proportional hazards model was used to assess the effect of SLE on the risk of hip fractures, adjusting for other risk factors at baseline only. In this analysis, the SLE diagnosis was considered the primary exposure, using a binary time-dependent variable with its value changing from 0 at the study entry date to 1 at the time of SLE diagnosis and afterward. All multivariable Cox models were adjusted for age and sex as well as other baseline covariates (i.e., rural or urban, neighborhood income quintile, health resource utilization, alcoholism, hypertension, ischemic heart disease, COPD-related diseases, depression, malignancy, Charlson Comorbidity Index score, NSAIDs, COX-2 inhibitors, HRT, glucocorticoids, anticoagulant therapy, other cardiovascular drugs excluding anticoagulant therapy, fibrates or statins, and antidiabetes medication). Thus, the HR estimate for the primary exposure variable captured the risk of hip fractures associated with the SLE condition that was independent of baseline risk factors. This Cox model did not include any time-varying risk factors during follow-up. As a result, the HR is confounded by the effect of other time-varying, nondisease-related factors, particularly glucocorticoid use during the follow-up period. Notably, when these time-varying risk factors were also intermediary variables from SLE to hip fractures, simply entering these time-varying risk factors as time-dependent covariates in the traditional multivariable Cox model would yield biased estimates of the true exposure effect (13,30). Moreover, fitting the traditional Cox model relies on the assumption of independent censoring. However, people experiencing censoring events may be systematically different in the time-varying risk factors from people who have not experienced censoring events; thus, ignoring dependent censoring can bias the HR estimates in the standard multivariable time-dependent Cox models.

To account for potential biases, analyses were conducted using a marginal structural Cox model (13), which is a class of causal models designed to properly adjust for time-dependent confounders that may also be mediators (e.g., glucocorticoid use), as well as to adjust for dependent censoring when evaluating the independent impact of SLE on the risk of hip fractures. Unlike traditional time-dependent Cox models, in marginal structural Cox models, pooled logistic regression models were used as the first step, with SLE status at each block as the dependent variable, and with time-varying and baseline covariates as predictors to obtain the inverse probability of exposure weights for each person-block. Using censoring status at each block as the dependent variable, the same procedure as above was applied to calculate the inverse probability of censoring weights. Then, a generalized estimating equation approach was used to estimate the risk of hip fracture using the inverse probability of exposure and censoring weights. As a result, the marginal structural Cox model yielded valid HR estimates for SLE-associated hip fracture risk that accounted
for mediators (13,14). SAS software, version 9.4, was used for all analyses, and for all HRs, 95% CIs were calculated.

**Ethics approval.** No personal identifying information was made available as part of this study. Procedures were in compliance with BC’s Freedom of Information and Protection of Privacy Act. Ethics approval was obtained from the University of British Columbia’s Behavioral Research Ethics Board (H15-00887).

**RESULTS**

**Baseline characteristics.** After excluding individuals who had prior hip fractures and other pathologic conditions prior to the study entry date, 5,047 patients with SLE (86% female, mean age 40 years) and 25,235 individuals without SLE (86% female, mean age 40 years) were identified up to the end of the follow-up period (March 31, 2015). Patients with SLE were matched with corresponding non-SLE individuals based on age, sex, and calendar year of SLE index date. Table 1 summarizes the baseline characteristics for both cohorts. Compared to the non-SLE cohort, the SLE cohort had more outpatient visits, rheumatologist visits, and hospitalizations, a larger Charlson Comorbidity Index score, and more preexisting comorbidities and medication use. All baseline covariates were assessed within 12 months prior to the study entry date rather than the SLE index date. Glucocorticoid and hydroxychloroquine use during the 12 months prior to the index date was also estimated: 39.6% and 60.6% of patients with SLE had used glucocorticoids and hydroxychloroquine, respectively.

**Risk of hip fracture in patients with SLE.** During the follow-up time after study entry, 73 incident hip fractures (mean follow-up time of 10.75 years) were observed in the SLE cohort, compared with 272 (mean follow-up time of 11.32 years) in the non-SLE cohort. The incidence rate for hip fractures in the SLE cohort was 0.93 events per 1,000 person-years, while the corresponding incidence rate in the non-SLE cohort was 0.69 events per 1,000 person-years. The cumulative incidence of hip fractures was significantly higher in the SLE cohort compared to the non-SLE cohort after accounting for the competing risk of death ($P < 0.001$ for log rank test) (Figure 1).

Cox proportional hazards models with SLE initiation as a time-dependent variable were used, and the multivariable models were adjusted for age, sex, and baseline covariates (i.e., rural or urban, neighborhood income quintile, health resource utilization, alcoholism, hypertension, ischemic heart disease, COPD-related diseases, depression, malignancy, Charlson Comorbidity Index score, NSAIDs, COX-2 inhibitors, HRT, glucocorticoids, anticoagulant therapy, other cardiovascular drugs excluding anticoagulant therapy, fibrates or statins, and antidiabetes medication). The corresponding HR was 1.86 (95% CI 1.37–2.52).

To further adjust for time-varying confounders after SLE diagnosis and dependent censoring, a marginal structural Cox model was created. The corresponding fully adjusted HR was 1.62 (95% CI 1.06–2.48) (Table 2). This risk estimate shows the direct role of SLE on hip fracture risk, independent of risk factors at baseline or during follow-up.

**DISCUSSION**

In this population-based study of a large incident SLE cohort, the overall risk of hip fractures was significantly higher following SLE diagnosis (HR 1.62 [95% CI 1.06–2.48]) after adjusting for baseline risk factors and time-varying variables, including

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLE cohort (n = 5,047)</th>
<th>Non-SLE (n = 25,235)</th>
</tr>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
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</tr>
<tr>
<td>Age, years</td>
<td>40.34 ± 14.81</td>
<td>40.47 ± 14.81</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>4,350 (86.19)</td>
<td>21,750 (86.19)</td>
</tr>
<tr>
<td>Rural, no. (%)</td>
<td>772 (15.30)</td>
<td>3,384 (13.41)</td>
</tr>
<tr>
<td>Neighborhood income quintile, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (lowest)</td>
<td>1,027 (20.35)</td>
<td>4,645 (18.41)</td>
</tr>
<tr>
<td>2</td>
<td>1,043 (20.67)</td>
<td>4,831 (19.14)</td>
</tr>
<tr>
<td>3</td>
<td>985 (19.52)</td>
<td>4,740 (18.78)</td>
</tr>
<tr>
<td>4</td>
<td>953 (18.88)</td>
<td>4,912 (19.47)</td>
</tr>
<tr>
<td>5 (highest)</td>
<td>856 (16.96)</td>
<td>4,866 (19.28)</td>
</tr>
<tr>
<td>Unknown</td>
<td>183 (3.63)</td>
<td>1,241 (4.92)</td>
</tr>
<tr>
<td>Health resource utilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of outpatient visits</td>
<td>17.94 ± 17.20</td>
<td>10.97 ± 12.44</td>
</tr>
<tr>
<td>No. of hospitalizations</td>
<td>0.2600 ± 0.7745</td>
<td>0.1570 ± 0.5138</td>
</tr>
<tr>
<td>No. of rheumatologist visits</td>
<td>0.0816 ± 0.5896</td>
<td>0.0062 ± 0.4193</td>
</tr>
<tr>
<td>Comorbidities, no. (%)</td>
<td></td>
<td></td>
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<tr>
<td>Alcoholism</td>
<td>26 (0.52)</td>
<td>121 (0.48)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>392 (7.77)</td>
<td>1,734 (6.87)</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>16 (0.32)</td>
<td>41 (0.16)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>188 (3.72)</td>
<td>459 (1.82)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (0.22)</td>
<td>19 (0.08)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>23 (0.46)</td>
<td>63 (0.25)</td>
</tr>
<tr>
<td>COPD-related diseases</td>
<td>438 (8.68)</td>
<td>1,624 (6.44)</td>
</tr>
<tr>
<td>Depression</td>
<td>539 (10.68)</td>
<td>1,866 (7.39)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>54 (1.07)</td>
<td>349 (1.38)</td>
</tr>
<tr>
<td>Charlson comorbidity index score</td>
<td>0.3037 ± 0.6469</td>
<td>0.1348 ± 0.4367</td>
</tr>
<tr>
<td>Medications, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs and COX-2 inhibitors</td>
<td>1,372 (27.18)</td>
<td>3,757 (14.89)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>501 (9.93)</td>
<td>1,488 (6.24)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>599 (11.87)</td>
<td>678 (2.69)</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>44 (0.87)</td>
<td>94 (0.37)</td>
</tr>
<tr>
<td>CVD drugs excluding anticoagulant therapy</td>
<td>550 (10.90)</td>
<td>1,896 (7.51)</td>
</tr>
<tr>
<td>Fibrates/statins</td>
<td>86 (1.70)</td>
<td>493 (1.95)</td>
</tr>
<tr>
<td>Antidiabetes medications</td>
<td>76 (1.51)</td>
<td>389 (1.54)</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD unless indicated otherwise. All baseline characteristics were measured over 12 months prior to the study entry date (start of follow-up). COPD = chronic obstructive pulmonary disease; COX-2 = cyclooxygenase-2; CVD = cardiovascular disease; NSAIDs = nonsteroidal antiinflammatory drugs; SLE = systemic lupus erythematosus.
Glucocorticoid use and health resource utilization. As proposed by previous studies, the etiology of bone loss and the occurrence of clinical fractures in SLE are likely to be multifactorial, involving both nondisease- and disease-related factors (3). Disease activity and potential therapeutic strategies, especially glucocorticoid use, may play a role in bone degradation. High systemic inflammation in severe SLE may contribute to bone loss by increasing osteoclastic bone resorption and by reducing osteoblastic bone formation (31). In patients with active disease, elevated serum levels of tumor necrosis factor (TNF) (32) and oxidized low-density lipoprotein (LDL) (33) are demonstrated. Oxidized lipids can activate T-cells, which increase production of RANKL and TNF. Both RANKL and TNF increase the maturation and activity of osteoclasts (32). Moreover, oxidized LDL also negatively influences bone formation by reducing osteoblast maturation (34). Decreased serum levels of osteocalcin, a marker of bone formation, and increased crosslinks excretion in the urine, which is considered a marker for bone resorption, were demonstrated in premenopausal women with recently diagnosed, untreated SLE (35).

Glucocorticoids are used extensively for the treatment of inflammation associated with SLE flares, and in 5 in 5 patients treated with glucocorticoids may have an osteoporotic fracture within the first year of treatment (36). Glucocorticoids are associated with negative consequences on bone health, including a decrease in vitamin D levels, by suppressing intestinal calcium absorption (37). Toloza et al found an association between cumulative glucocorticoid exposure and low serum levels of both 25(OH)D and 1,25(OH)2D (37). Moreover, high-dose glucocorticoid use may have a negative effect on bone density by stimulating bone resorption and reducing bone formation via increasing osteoblast and osteocyte apoptosis (36). Therefore, adjusting for glucocorticoids using a method that can properly handle both the baseline use and the use during follow-up (intermediary variable) is crucial when assessing the independent risk of osteoporotic fractures associated with SLE.

The current study's findings of an increased risk of hip fractures after SLE diagnosis are consistent with previous studies (4,7,9,11,12). However, only 1 study from the UK has attempted to adjust for the effects of time-varying covariates using the standard time-dependent Cox proportional hazards model, and their findings were not statistically significant (HR 1.09 [95% CI 0.65–1.82]) (8). As discussed above, unlike the current study, the standard time-dependent Cox model used in the UK study cannot properly adjust for time-dependent confounders that are also mediators (i.e., glucocorticoids). Moreover, that study did not account for the effect of dependent censoring due to competing events, such as death (29). These limitations may explain the substantially smaller effect size and statistically nonsignificant association.

Some limitations of this study must be acknowledged. The uncertainty of the accuracy of the SLE case definition cannot be completely ruled out, even though a stringent algorithm requiring at least 2 principal codes for SLE at least 2 months apart within 2 years was used. Misclassification could possibly still occur, but this misclassification would be a conservative bias where the observed effect would be led toward the null. Nevertheless, 99.4% of patients with SLE in this study were diagnosed by rheumatologists or from hospitalizations. As shown in previous studies, the validity for SLE case definitions that include specialist visits and hospitalizations is very high (up to 98% for sensitivity and positive predictive value) (26,38).

Uncertainty about the ascertainment of the hip fracture case definition may also exist because the range of the positive predictive value in the previous validation study is very wide (63–96%) (27). However, a recommendation from a systematic review

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**Table 2.** Overall risk of hip fractures in patients with SLE relative to individuals without SLE during follow-up*

<table>
<thead>
<tr>
<th></th>
<th>SLE cohort (n = 5,047)</th>
<th>Non-SLE cohort (n = 25,235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hip fracture events</td>
<td>73</td>
<td>272</td>
</tr>
<tr>
<td>Incidence rate per 1,000 person-years</td>
<td>0.93</td>
<td>0.69</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI)</td>
<td>1.34 (1.02–1.75)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-, sex-, and baseline covariates adjusted†</td>
<td>1.86 (1.37–2.52)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-, sex-, baseline covariates, and weighted time-varying variables adjusted‡</td>
<td>1.62 (1.06–2.48)</td>
<td>1.00</td>
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</tbody>
</table>

* Values are the hazard ratio (95% confidence interval [95% CI]) unless indicated otherwise. SLE = systemic lupus erythematosus.
† Adjusted for rural or urban, neighborhood income quintile, health resource utilization, alcoholism, hypertension, ischemic heart disease, chronic obstructive pulmonary disease–related diseases, depression, malignancy, Charlson Comorbidity Index score, nonsteroidal antiinflammatory drugs, and cyclooxygenase-2 inhibitors, hormone replacement therapy, glucocorticoids, anticoagulant therapy, other cardiovascular drugs excluding anticoagulant therapy, fibrates or statins, and antidiabetes medication.
suggests that ICD codes are valid to identify hip fractures but not vertebral fractures (27). All known risk factors for hip fractures available in our data were adjusted for; however, some risk factors, such as body mass index and smoking history, were not available in the data set. The absence of ethnicity in the databases is also a limitation because ethnicity may influence hip fracture risk (39).

Certainly, evaluating the effect of having SLE on the risk of complications, such as hip fracture, can be challenging. It is unethical or impossible to manipulate or assign disease conditions to patients to study the SLE effect on hip fractures via randomized clinical trials. Therefore, applying the marginal structural model in this setting may not truly estimate the causal effect of SLE on hip fractures since SLE status is not assigned. However, a comparable example is found in a study that evaluated the effect of systolic blood pressure level on the time to renal event (14), in which one cannot assign systolic blood pressure level to patients. In these situations, one must rely on observational data. In our study, state-of-the-art marginal structural model methods were applied to study the effect of having SLE on the risk of hip fractures. The validity of the effect estimate requires the assumption that there are no unobserved confounders, and given the set of baseline and time-varying confounders included in this analysis, the marginal structural model would be satisfied.

Despite these limitations, there are several strengths. A large Canadian administrative data set based on the entire BC population was used, which makes the findings generalizable. Additionally, this is also the first study assessing the risk of hip fractures in SLE after accounting for the impact of time-varying covariates by using a marginal structural Cox model (13). This model can properly adjust for both time-dependent confounders that may also be mediators and dependent censoring. Furthermore, we required at least 7 years of run-in time before the first ICD code for SLE to only include true incident patients and exposures, which avoids the survival bias of using a prevalent cohort.

In summary, this population-based study demonstrates that patients with SLE have an approximately 60% increased risk of sustaining a hip fracture compared to the general population. This result expands on the findings of previous studies and has important implications for the prevention, screening, and treatment of osteoporosis that may lead to hip fractures. Further studies should clarify the impact of inflammation, glucocorticoid dosage, and duration of use on the risk of hip fractures among patients with SLE.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Aviña-Zubieta had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Li, Xie, Esdaile, Aviña-Zubieta.

Acquisition of data. Li, Xie, Lu, Aviña-Zubieta.

Analysis and interpretation of data. Li, Xie, Lu, Esdaile, Aviña-Zubieta.

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