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Incidence of and Risk of Mortality After Hip Fractures in Rheumatoid Arthritis Relative to the General Population

C. Allyson Jones,[1] Pierre Guy,[2] Hui Xie,[3] Eric C. Sayre,[4] Kai Zhao,[3] and Diane Lacaille[5]

Objective. Osteoporosis, a known complication of rheumatoid arthritis (RA), increases the risk of hip fracture, which is associated with high morbidity and mortality. Fracture risk estimates in patients with RA treated with contemporary treatment strategies are lacking. The objectives were (1) estimate age-specific and sex-specific incidence rates and compare the risk of hip fractures in RA relative to age-matched and sex-matched general population controls, and (2) compare the risk of all-cause mortality in RA and general population controls after hip fracture.

Methods. A longitudinal study of a population-based incident cohort of patients with RA diagnosed between 1997 and 2009, followed until 2014, with age-matched and sex-matched controls from the general population of British Columbia, using administrative health data. Hip fracture outcomes (International Classification of Diseases, Ninth Edition, Clinical Modification [ICD-9-CM] codes 820.0 or 820.2; ICD-10-Canada code S72.0 to S72.2) and mortality at predefined intervals after fracture (in hospital, 90 days, 1-year, 5-year) were identified. Hip fracture incidence rates for RA and controls, and incidence rate ratios (IRRs), were calculated. Cox proportional hazards models compared hip fracture and mortality risk in RA versus controls; logistic regression compared in-hospital mortality risk.

Results. Overall, 1,314 hip fractures over 360,521 person-years were identified in 37,616 individuals with RA and 2,083 over 732,249 person-years in 75,213 controls, yielding a 28% greater fracture risk in RA (IRR 1.28 [95% confidence interval 1.20–1.37]). Mean age at time of fracture was slightly younger for RA than controls (79.6 ± 10.8 vs 81.6 ± 9.3 years). Postfracture mortality risk at one-year and five-years did not differ between RA and general population controls. Results were similar in a sensitivity analysis including only individuals with RA who received disease-modifying antirheumatic drugs.

Conclusion. People with RA had a greater risk of hip fractures, but no greater risk of mortality post fracture, than the general population. The relative risk of hip fractures observed was not as high as previously reported, likely reflecting better treatment of inflammation and management of osteoporosis and its risk factors.

INTRODUCTION

Rheumatoid arthritis (RA) is associated with fragility fractures and is the only disease that is specifically identified as a risk factor for fracture within the Fracture Risk Assessment Tool (FRAX).[1] Although vertebral fractures account for half of fragility fractures in RA,[2] hip fracture is a public health burden because of the high morbidity, mortality, disability, and socioeconomic costs.[3,4] Hip fractures have been extensively studied in older patient populations, yet a paucity of literature has examined hip fracture in RA despite osteoporosis affecting slightly more than 25% of the RA population.[5] The burden of hip fracture cannot be underestimated. Within the general population, temporal and geographic variations of incidence rates exist worldwide with an estimated incidence rate of 14.2 (95% confidence interval [95% CI] 11.1–18.1) per 1,000,000 in 2019.[6] In Canada, the national age and sex standardized incidence rate is 15.78 (95% CI 15.72–15.83) per 1,000,000.[7] The one-year mortality rates after

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[1]C. Allyson Jones, PT, PhD: University of Alberta, Edmonton, Alberta, and Arthritis Research Canada, Vancouver, British Columbia, Canada; [2]Pierre Guy, MD, MBA, FRCSC: University of British Columbia, Vancouver, British Columbia, Canada; [3]Hui Xie, PhD, Kai Zhao, MSc: Arthritis Research Canada, Vancouver, and Simon Fraser University, Burnaby, British Columbia, Canada; [4]Eric C. Sayre, PhD: Arthritis Research Canada, Vancouver, British Columbia, Canada; [5]Diane Lacaille, MD, FRCPC, MHSc: Arthritis Research Canada and University of British Columbia, Vancouver, British Columbia, Canada.

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Address correspondence via email to Diane Lacaille, MD, FRCPC, MHSc, at dlacaille@arthritisresearch.ca.

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SIGNIFICANCE & INNOVATIONS

- Rheumatoid arthritis (RA) is a risk factor for fragility fractures including hip fractures.
- Hip fracture is a public health burden with high morbidity and mortality risk.
- Relative risk of hip fractures observed was not as high as historically reported, likely reflecting better treatment of inflammation and management of osteoporosis and its risk factors.
- Nonetheless, the risk of hip fracture remains higher than in general population controls of the same age and sex, despite advances in treatment.
- Mortality after hip fracture did not differ significantly from that of general population controls for the same age and sex.
- Given the persistently increased risk of hip fractures despite advances in treatment of inflammation, and the high morbidity and mortality following hip fractures, fall prevention programs and other primary prevention strategies targeting RA are needed.

a hip fracture are high, ranging up to 35%.[7,8] The excess mortality rate is at least double for age-matched population norms with the greatest mortality risk within the first three to six months after the index hip fracture.[9,10] Recovery after hip fracture in the general population is long-term, lasting two or more years,[11] with many patients unable to return to independent community living.[4,11,12]

A recent systematic review reported the pooled incidence rate of hip fractures in RA of 4.33 (95% CI 2.26–8.27) per 1,000 person-years.[2] Moreover, the secular trend of hip fracture in RA populations is increasing,[13] unlike the static or decreasing trends reported in the general population.[3,7] This epidemiologic pattern of hip fracture was illustrated in a Spanish cohort, in that patients with RA tended to be younger than the general population, and the incidence of hip fracture in the RA cohort increased over the 17 year observation period.[13] Mortality is high after a hip fracture, yet mortality is not commonly reported in RA cohorts with hip fractures.[13–15] There is consistent evidence, however, that mortality post hip fracture is greater in men than women regardless of whether a patient has RA or not.[7, 15]

Although hip fracture in RA has been examined across different geographic regions and ethnicities, several studies have evaluated risk in prevalent RA cohorts, which can provide biased risk estimates.[2,16] The methodology is inconsistent in terms of study designs, case ascertainment, and reporting fractures, all of which may account for the varied incidence rates reported in the literature. Assembling a population-based cohort of incident RA followed from diagnosis will provide a reliable estimate of hip fracture risk relative to the general population. The objectives of this study are two-fold: (1) to estimate age-specific and sex-specific incidence rates and compare the risk of hip fractures in RA relative to age-matched and sex-matched general population controls, and (2) to compare the risk of all-cause mortality in RA and general population controls after a hip fracture.

METHODS

Study design and sample. A longitudinal study of a population-based incident RA cohort with age-matched and sex-matched general population controls using administrative health data for the province of British Columbia (BC), Canada.

Incident RA cohort. An incident cohort of persons with RA was identified using a previously published RA definition.[17] Using physician billing data, all incident patients with RA in BC who first met RA criteria between January 1, 1997, and December 31, 2009, were identified and followed until December 31, 2014. The case definition included having a minimum of two physician visits more than two months apart, within a five-year period, with International Classification of Diseases, Ninth Edition (ICD-9) codes for RA (714.X) and/or the Tenth version (ICD-10-Canada: M05.X–M06.X). The rationale for two visits rather than a single visit was to avoid cases in which an initial impression of RA, or a visit to evaluate for possible RA, was not confirmed on later visits. The reasoning for the two physician visits being more than two months apart was to exclude transient inflammatory arthritis. Individuals were excluded if, over a five-year period after their second RA visit (ie, RA index date), they had at least two subsequent visits, on two different days, with the same diagnostic code for another form of inflammatory arthritis (systemic lupus erythematosus, other connective tissue diseases, psoriatic arthritis, ankylosing spondylitis, and other spondyloarthropathies); or if a diagnosis of RA by a nonrheumatologist was never confirmed during subsequent visits to a rheumatologist. These criteria have been validated in a subsample who participated in a RA survey, using opinion of an independent rheumatologist reviewing medical records from their treating physicians as gold standard, yielding a positive predictive value (PPV) of 0.82.[18] Date of the second ICD code for RA diagnosis was used as the RA index date. To identify incident cases, a run-in period of seven years was used (selected to have the longest run-in period possible, because the earliest data available were from 1990 onward). This ensured prevalent cases of RA who moved to BC were not erroneously identified as incident RA cases, by excluding individuals with RA with less than seven years of available data in Medical Service Plan (MSP) registry prior to their first RA visit.

Matched general population controls. A random control sample without any diagnosis of RA or other inflammatory arthritis was assembled from the general population (BC population was 3.9–4.4 million in 1997–2009[19]) using the same administrative databases as for the RA cohort. Controls were matched to individuals with RA using a 2:1 ratio on birth year, sex, and calendar year of MSP enrollment, and were assigned the same RA index date as the corresponding RA case.

Exclusion criteria applied to the RA cohort and general population controls included hip fractures, pathologic fractures, or Paget's disease occurring at any time prior to RA index date (or index date in controls), using all available data from 1990 onward. To minimize the possibility of missing prior hip fractures and inadvertently classifying a second hip fracture as an incident hip fracture in individuals who moved to BC, a run-in period of seven years was used, whereby individuals with less than seven years of data prior to (RA) index date were excluded.

Data sources. Complete health information for physician visits, medications dispensed, and hospitalizations were obtained from administrative databases of the Ministry of Health, through Population Data BC until December 2014. Within this public health care system, all persons are guaranteed universal coverage for physician visits and hospital and medical services, including surgical treatment of hip fracture. Our specific data sources are listed below:

1. Canadian Institute of Health Information Hospital Separation Abstracts (January 1990 to December 2014)[20] include up to 25 diagnostic codes per hospitalization using full five-digit ICD-9 and/or ICD-10 codes, representing either the reason for admission or complications during hospitalization, hospital admission and discharge dates, and hospital transfers. One hundred percent of hospitalizations in BC are captured through this system.
2. MSP File (January 1990 to December 2014)[21] contains physician claims data used for reimbursement of physician visits, under fee-for-service billings. Each claim contains a single diagnosis representing the reason for the visit based on ICD-9 diagnostic codes. Approximately 95% of physician-patient episodes of care in BC are reimbursed through the BC Ministry of Health fee-for-service.
3. MSP Consolidation File (January 1990 to December 2014)[21] includes demographic information for each person registered with the provincial plan, such as age, sex, postal code (first three digits) used to determine rural versus urban residence, neighborhood income quintile and local health area, and registration data.
4. BC Vital Statistics (January 1996 to December 2014)[22] were obtained on the date of death and primary cause of death (ICD-9 or ICD-10) from information provided on death certificates.
5. Pharmanet Database (January 1996 to December 2014)[23] provides information on all prescriptions dispensed by pharmacies in BC, regardless of source of funding.

Hip fracture outcomes were identified using ICD9-CM codes 820.0 or 820.2 and ICD10-Canada code S72.0 to S72.2 placed in any position in hospitalization data, representing either the reason for admission or a complication occurring during hospitalization.[24, 25] The accuracy of this algorithm to identify hip fractures from administrative data has been validated when used with hospital data (sensitivity 83%–97%; PPV 86%–98%).[26] This approach also ensured that we captured hip fractures that may have occurred while in hospital for other reasons.[27] Pathologic fractures (metastases; disorders of bone such as Paget's disease, fractures of other or unspecified femur location or acetabular-pelvic fractures) were not included.

Mortality outcomes. All-cause mortality was assessed at predetermined time points: in hospital, 90-day, 1-year and 5-year post fracture to capture short and long-term complications of hip fractures. Although not all deaths post hip fracture may be directly attributable to fractures,[28] we opted to evaluate all-cause mortality to capture the broadest impact of hip fracture on people's health that can contribute to increased mortality. The definition of an episode of care as outlined by Sheehan et al was used to assess in-hospital mortality, to take into consideration hospital transfers.[29]

Covariates. Baseline covariates were assessed within 12 months prior to RA index date in the analyses evaluating risk of hip fracture, and within 12 months prior to hip fracture date in the analyses evaluating mortality risk post hip fracture. Covariates included age, sex, social economic status (SES) based on the first three postal code digits and neighborhood income quintile, urban/rural area, the Romano modification of the Charlson comorbidity index (excluding RA from comorbidities) for use with administrative data (cardiovascular disease including coronary artery disease, congestive heart failure, peripheral vascular disease, venous thromboembolism; respiratory conditions; dementia; depression; malignancy; cerebrovascular accident; chronic liver disease/cirrhosis; alcoholism; chronic kidney disease),[30–32] and hospital size for postfracture mortality analyses. A single diagnostic code (ICD-9/10) in hospitalization data and physician service claims were used to identify comorbidities (see Supplementary Table 1).

Statistical analysis. Descriptive statistics (ie, means, SDs, or frequency counts and percentages) were computed for relevant variables in the RA cohort and general population controls. Incidence rates of hip fractures were calculated for the RA cohort and general population controls, and risk of hip fracture in RA relative to the general population was estimated using crude incidence rate ratios (IRR) with 95% CIs, and adjusted hazard ratios (aHRs) from Cox's proportional hazard models (PHMs) adjusted for age, sex, and Romano Charlson (excluding RA). For each individual, follow-up started at (RA) index date and ended at occurrence of first hip fracture, with censoring of follow-up at time of death, out-of-province migration, or end of follow-up (December 2014), whichever occurred first. Covariates were selected for inclusion as potential confounders in the final PHMs according to a purposeful selection algorithm using a 5% threshold for inclusion. The algorithm proceeded by entering potential confounders one at a time into the PHM, and assessing the relative change in the

HR estimating fracture risk in RA relative to the general population, compared with the previous model.[33] The algorithm stopped when no additional variables had a ≥5% impact on the HR for RA.[33,34] Alternative models were fit based on the subdistribution hazards to accommodate for the competing risk of death.[35] By comparing results from the subdistribution hazards regression model and Cox's PHMs, the two primary statistical models for competing risk analysis, we evaluated the robustness of adjusted HR estimates across different modeling methods. We also used the Fine-Gray method[36] to compute the cumulative incidence function (CIF) of first hip fracture, while accounting for competing risks of death because of causes unrelated to hip fracture. Gray's Test[37] was used for comparing the CIFs between the two groups.

Mortality post hip fracture was analyzed via Cox PHMs in all RA and general population patients who sustained a hip fracture. For each individual, follow-up started at fracture date and ended at occurrence of death, with censoring of follow-up at out-of-province migration or end of follow-up (December 2014), whichever occurred first. We fit unadjusted models, models adjusted for age and sex, and models adjusted for age, sex, SES, rural/urban, hospital size, and fracture type. With the sensitivity analyses, we also fit models adjusted for age, sex, SES, rural/urban area, hospital size, fracture type, and the following comorbidities influencing risk of death: Romano Charlson (excluding RA), cardiovascular disease, chronic obstructive pulmonary disease (COPD), malignancy, dementia, alcoholism, diabetes, hyperlipidemia, Hormonal Replacement Therapy, and anticoagulants. Although matching variables age and sex were not confounders, they are known strong predictors of the outcomes, and adjusting for them increases the power to detect between group differences. Each model estimated the effects of RA (vs general population) on mortality according to time since fracture: <90 days, 90 days to 1 year, and 1 to 5 years post fracture. In addition, we computed cumulative all-cause mortality, using product limit estimates, at 90-day, 1-year, and 5-year post fracture, stratified by RA status. In-hospital mortality (binary yes/no variable) was estimated using logistic regression models. Sensitivity analyses were also conducted limiting the sample to individuals with RA who had received disease-modifying antirheumatic drugs (DMARDs) and their age-matched and sex-matched controls to ensure that hip fracture and mortality risks relative to the general population controls were not affected by our RA definition, which did not require specific RA treatment. Analyses were performed using SAS version 9.4 (SAS Institute Inc). Ethics approval was obtained from the Health Research Ethics Review Board at the University of British Columbia (H00-80305) and University of Alberta (PRO 00071977).

RESULTS

A total of 37,616 persons with RA and 75,213 age/sex-matched general population controls were followed from January 1, 1997, to December 31, 2014. The sample included 66% females, and the mean (SD) age at RA diagnosis was 57.3 (16.6) years (Table 1). Within the RA cohort, hydroxychloroquine (30.0%) and methotrexate (26.3%) were the most commonly dispensed DMARDs, followed by sulfasalazine (13%) and leflunomide (6%), whereas 6.2% received biologics. Over 360,521 person-years of follow-up, 1,314 hip fractures occurred in the RA cohort (mean [SD] follow-up time: 9.6 [4.3] years), whereas 2,083 hip fractures were reported over 732,249 person-years of follow-up for the matched general population controls (mean [SD] follow-up time: 9.7 [4.3] years), yielding incident rates per 1,000 person-years of follow-up of 3.6 (95% CI 3.4–3.8) in RA and 2.8 (95% CI 2.7–3.0) in general population controls. The mean (SD) age at time of hip fracture was slightly younger for the RA cohort than the general population controls (79.5 [10.8] vs 81.6 [9.3] years; $P < 0.001$). At the time of hip fracture, the RA cohort had more comorbidities than controls, as reflected by a higher mean (SD) Romano comorbidity score (RA: 1.3 [1.8] vs control: 1.08 [1.1]; $P = 0.002$). The most frequent comorbidity reported in both groups at the time of hip fracture was cardiovascular diseases (RA 62%; control 63%), whereas chronic obstructive lung conditions (COPD, emphysema, chronic bronchitis, asthma) (18%) was the next most reported comorbidity for the RA group and dementia (23%) for the control group.

Fracture characteristics and surgical management. No differences were seen between the two groups in the type of hip fracture; slightly less than one-half of both groups had transcervical hip fractures (Table 1). Approximately 23% in both groups were transferred to another hospital for surgery, and 7% in both groups did not receive surgery after admission for hip fracture. The median (25th, 75th percentile) time from hospital admission to surgery was 1.0 (1.0, 2.0) days for both groups. More people with RA resided in rural locales (16.8%) than general population controls (11.6%) at the time of hip fracture, with a greater number of patients with RA hospitalized in smaller hospitals (Table 1).

Risk of hip fracture. The crude IRR for hip fractures was 1.28 (95% CI 1.20–1.37) (Figure 1), indicating that individuals with RA had a 28% higher risk of hip fractures than general population controls. The IRR was slightly higher in males than females (1.45 [95% CI 1.25–1.69] vs 1.24 [95% CI 1.14–1.34]), although the difference was not statistically significant. The IRR for hip fracture decreased with increasing age. Individuals diagnosed with RA before the age of 60 had a greater than two-fold increase in risk of hip fracture, whereas the increased risk was less than two-fold for individuals diagnosed after the age of 60. The risk did not differ significantly from general population controls in individuals diagnosed after the age of 80 (Figure 1).

Multivariable Cox PHMs estimating the risk of incident hip fracture in RA relative to general population controls, age-adjusted and sex-adjusted HR was 1.28 (95% CI 1.19–1.37) (Table 2). In the final fully adjusted model, the Romano comorbidity score was the only additional covariate selected. The Cox PHM

Table 1. Characteristics of incident RA cohort and general population controls*

	RA	Controls	*P* value
n	37,616	75,213	—
Person-years of follow-up	360,521	732,249	—
Female, n (%)	24,987 (66)	49,880 (66)	0.717
Age at index date,[a] mean (SD), y	57.3 (16.6)	57.2 (16.6)	0.771
Hip fractures, n (%)	1,314 (3.5)	2,083 (2.8)	**<0.001**
Incidence rate per 1,000 person-years (95% CI)	3.6 (3.4–3.8)	2.8 (2.7–3.0)	**<0.001**
Hip fracture characteristics			
Age at hip fracture, mean (SD), y	79.5 (10.8)	81.6 (9.3)	**<0.001**
Female, n (%)	1,019 (77.6)	1,667 (80.0)	0.084
Type of hip fracture, n (%)			0.899
Cervical	626 (47.6)	997 (47.9)	—
Trochanteric[b]	688 (52.4)	1,086 (52.1)	—
Type of surgical fixation, n (%)			0.976
Total hip arthroplasty	46 (3.5)	70 (3.4)	—
Hemiarthroplasty	143 (10.9)	222 (10.7)	—
Internal fixation	1,031 (78.5)	1,635 (78.5)	—
No surgery	94 (7.2)	156 (7.5)	—
Chronic conditions[c]			
Cardiovascular disease	816 (62.1)	1,308 (62.8)	0.684
Respiratory conditions	243 (18.5)	306 (14.7)	**0.003**
Dementia	230 (17.5)	475 (22.8)	**<0.001**
Depression	200 (15.2)	292 (14.0)	0.332
Cancer and malignancy	143 (10.9)	202 (9.7)	0.265
Cerebrovascular accident	92 (7.0)	149 (7.2)	0.867
Chronic liver disease/cirrhosis	37 (2.8)	38 (1.8)	0.055
Romano score,[d] mean (SD)	1.3 (1.8)	1.1 (1.5)	**0.002**
LOS, median (25Q–75Q), d	15 (8–31)	16 (8–33)	0.635
Hospital size for hip surgery			**<0.001**
<50 beds	100 (7.6)	127 (6.1)	—
50–199 beds	474 (36.1)	613 (29.4)	—
200+ beds	740 (56.3)	1,343 (64.5)	—
Hospital transfer, n (%)	306 (23.3)	484 (23.2)	0.972
Residence locale at hip fracture time			**<0.001**
Rural	221 (16.8)	241 (11.6)	—
Urban	1,093 (83.2)	1,842 (88.4)	—
Socioeconomic status quintile of neighborhood at hip fracture time			0.767
1, lowest	351 (26.7)	547 (26.3)	—
2	273 (20.8)	409 (19.6)	—
3	261 (19.9)	408 (19.6)	—
4	221 (16.8)	384 (18.4)	—
5, highest	208 (15.8)	335 (16.1)	—

Note: The bolded *p*-values denotes statistical significance.
* *Source*: Unless otherwise indicated, values represent n (%). 95% CI, 95% confidence interval; LOS, length of stay; Q, quarter; RA, rheumatoid arthritis.
[a] Age at index date of RA diagnosis; control group was assigned the same index date as the corresponding RA cases.
[b] Pertrochanteric or subtrochanteric hip fracture.
[c] Chronic conditions and Romano scores evaluated within 12 months prior to the date of hip fracture.
[d] Romano adaptation of Charlson comorbidity index developed for administrative health data, excluding RA as a comorbidity.

adjusted for age, sex, and Romano score estimated that persons with RA had a 27% greater risk of hip fracture than general population controls (aHR 1.27 [95% CI 1.18–1.36]); the relative risk was greater for males than females (aHR 1.44 [95% CI 1.24–1.67] vs aHR 1.23 [95% CI 1.13–1.33]) (Table 2), although the difference was not statistically significant. Cox PHMs stratified by age showed similar trends in risk relative to the general population according to age as described above for the IRR results. Alternative analysis accounting for competing events using different approaches yielded similar results attesting to the robustness of our findings. Specifically, when looking at the cumulative incidence of hip fracture, accounting for the competing risk of death, persons with RA had a statistically significant higher risk and shorter time to acquire a first hip fracture than general population controls (Gray's test *P* value <0.001) (Figure 2). Subdistribution PHMs accounting for the competing risks of death did not produce substantially different estimates compared with the standard cause-specific PHMs (Table 2).

Risk of mortality post hip fracture. A total of 715 deaths post hip fracture were observed in the RA cohort and 1,224 in the general population controls (Table 3). Of the

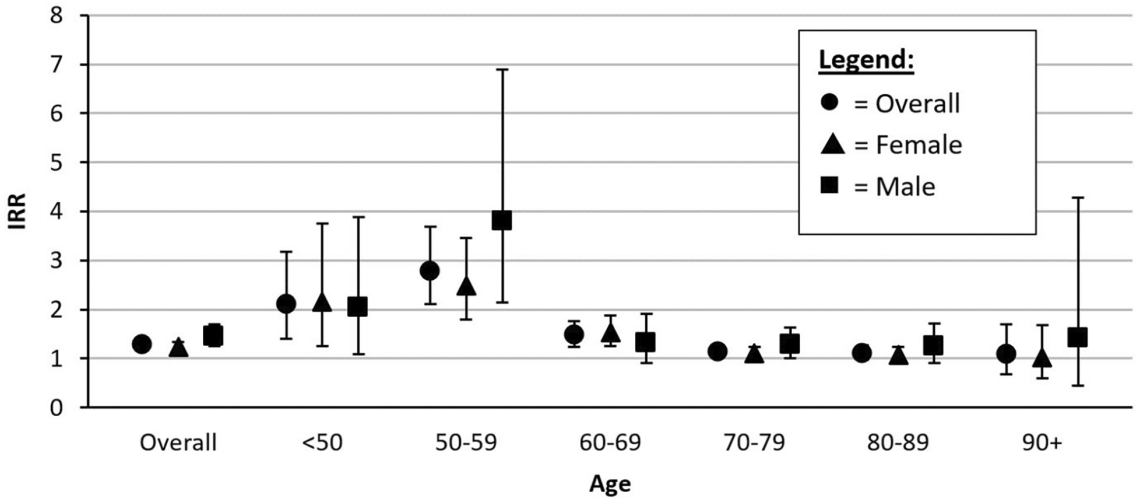

Figure 1. IRRs of hip fracture in rheumatoid arthritis versus controls, by age and sex. IRR, incidence rate ratio.

Table 2. PHM and sHR estimating risk of hip fracture in RA relative to general population controls*

	Overall		Females		Males	
Cox PHMs	cHR (95% CI)	sHR (95% CI)	cHR (95% CI)	sHR (95% CI)	cHR (95% CI)	sHR (95% CI)
Unadjusted models	1.29 (1.20– 1.38)	1.27 (1.18– 1.36)	1.24 (1.15–1.34)	1.22 (1.13–1.32)	1.46 (1.26–1.69)	1.43 (1.23–1.66)
Age- and sex-adjusted models	1.28 (1.19–1.37)	1.26 (1.17–1.35)	1.23 (1.14–1.33)	1.22 (1.12–1.32)	1.46 (1.26–1.69)	1.43 (1.23–1.66)
Fully adjusted models[a]	1.27 (1.18–1.36)	1.26 (1.17–1.35)	1.23 (1.13–1.33)	1.23 (1.12–1.32)	1.44 (1.24–1.67)	1.43 (1.23–1.66)
Fully adjusted models stratified by age						
<50 y	2.06 (1.39–3.04)	2.03 (1.37–3.00)	2.08 (1.24–3.50)	2.09 (1.25–3.49)	2.00 (1.11–3.62)	1.95 (1.07–3.57)
50–59 y	2.72 (2.07–3.56)	2.69 (2.05–3.52)	2.47 (1.80–3.37)	2.44 (1.78–3.33)	3.57 (2.06–6.16)	3.54 (2.05–6.12)
60–69 y	1.47 (1.23–1.74)	1.44 (1.21–1.71)	1.51 (1.24–1.84)	1.49 (1.23–1.82)	1.32 (0.92–1.90)	1.28 (0.90–1.83)
70–79 y	1.14 (1.03–1.27)	1.13 (1.01–1.26)	1.11 (0.98–1.25)	1.09 (0.97–1.23)	1.29 (1.02–1.63)	1.28 (1.01–1.61)
80–89 y	1.10 (0.96–1.25)	1.11 (0.98–1.27)	1.07 (0.93–1.23)	1.09 (0.94–1.25)	1.24 (0.91–1.69)	1.25 (0.92–1.71)
90+ y	1.12 (0.72–1.73)	1.03 (0.67–1.59)	1.06 (0.65–1.74)	0.98 (0.61–1.59)	1.39 (0.51–3.75)	1.27 (0.46–3.47)

* *Source*: 95% CI, 95% confidence interval; cHR, cause-specific hazard ratio; PHM, proportional hazard model; RA, rheumatoid arthritis; sHR, subdistribution hazard ratio, which accounts for competing risk of death.
[a] Adjusted for age, sex, and Romano comorbidity score (excluding RA).

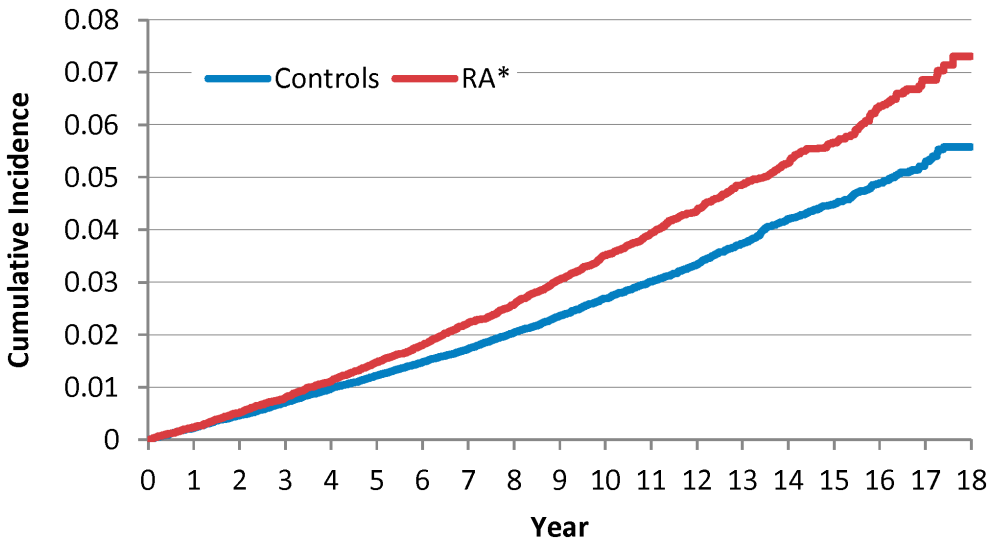

Figure 2. Cumulative incidence functions of hip fracture among RA and controls, adjusting for death as competing events. *Significant difference *P* value <0.001 (Gray's test). RA, rheumatoid arthritis.

Table 3. All-cause mortality after hip fracture*

Characteristics of people who died	RA	Controls	*P* value
Number of deaths	715	1,224	—
Age at death, mean (SD), y	84.8 (8.9)	86.2 (7.6)	**0.009**
Females, n (%)	537 (75.1)	960 (78.4)	0.092
Rural, n (%)	123 (17.2)	133 (10.9)	**<0.001**
Hospital LOS, median (IQR)	18 (9–36)	19 (9–37)	0.782
Socioeconomic status quintile of neighborhood at time of hip fracture			0.125
1 lowest	197 (27.6)	338 (27.6)	—
2	161 (22.5)	230 (18.8)	—
3	116 (16.2)	248 (20.3)	—
4	131 (18.3)	215 (17.6)	—
5 highest	110 (15.4)	193 (15.8)	—
Time from fracture to death, median (IQR), d	764 (156–1,518)	631 (107–1,415)	**0.035**
Cumulative number (%) deaths			—
In-hospital death	94 (13.1)	182 (14.9)	0.295
Death ≤90 d	137 (19.2)	284 (23.2)	**0.006**[a]
Death ≤1 y	252 (35.2)	470 (38.4)	0.584[a]
Death ≤5 y	585 (81.8)	1,027 (83.9)	**0.021**[a]

Note: The bolded *p*-values denotes statistical significance.
* *Source*: IQR, interquartile range; LOS, length of stay; RA, rheumatoid arthritis.
[a] *P* values are from corresponding event time models.

patients who did not receive surgery, in-hospital mortality for individuals with RA was 26.6% (n = 25) and 29.5% (n = 46) for general population controls. Mean age at death was slightly younger for the RA cases than general population controls (84.8 [8.9] years vs 86.2 [7.6] years; $P = 0.009$). The 90-day mortality rate was lower in individuals with RA than general population controls (456.6 deaths per 1,000 person-years vs 610.4 deaths per 1,000 person-years; $P = 0.006$) (Table 3). The Cox PHM analyses adjusted for age, sex, and other sociodemographic factors potentially influencing postfracture mortality (ie, SES, rural/urban location, hospital size, and fracture type); patients with RA had a 20% lower 90-day mortality risk relative to general population controls (aHR 0.80 [95% CI 0.65–0.98]) (Table 4). Sensitivity analyses in which a third model adjusted for the covariates included in adjusted model 2, as well as for comorbidities potentially influencing mortality risk, yielded similar results (adjusted model 3, Table 4). Otherwise, cumulative mortality rates and mortality risks over different time periods post hip fractures did not differ significantly between patients with RA and general population controls who sustained hip fractures (Tables 4).

Sensitivity analyses conducted on the subgroup of patients with RA who received DMARDs did not reveal substantial differences in results from the main analyses (see Supplementary Tables 2–5). The fully adjusted Cox PHM estimated that persons with RA who received DMARDs had a 41% greater risk of hip fracture than general population controls (aHR 1.41 [95% CI 1.26–1.59]), a risk only slightly higher than in the entire RA cohort (aHR 1.27 [95% CI 1.18–1.36]) (see Supplementary Table 3). Estimates of mortality post hip fracture were very similar to those of the entire RA cohort, and mortality risk post hip fracture did not differ significantly between patients with RA receiving DMARDs and general population controls (see Supplementary Table 5).

Table 4. Mortality risk in RA relative to general population controls after hip fracture*

Cumulative mortality	Mortality rate RA (per 1,000 PY)	Mortality rate controls (per 1,000 PY)	Period-specific HR	Unadjusted HR (95% CI)	Adjusted HR(1)[a] (95% CI)	Adjusted HR(2)[b] (95% CI)	Adjusted HR(3)[c] (95% CI)
In hospital	94/715[d]	182/1224[d]	In hospital[e]	0.80 (0.62–1.04)	0.86 (0.66–1.12)	0.84 (0.65–1.10)	0.82 (0.63–1.07)
90 d	456.6	610.4	<90 d	**0.75 (0.61–0.92)**	**0.81 (0.66–0.99)**	**0.80 (0.65–0.98)**	**0.78 (0.64– 0.96)**
1 y	228.3	280.5	90 d–1 y	0.94 (0.74–1.18)	1.01 (0.80–1.27)	1.0 (0.79–1.26)	0.96 (0.76–1.21)
5 y	161.2	194.1	1–5 y	**0.85 (0.74–0.98)**	0.93 (0.81–1.06)	0.92 (0.80–1.05)	0.89 (0.78–1.02)

Note: The bolded *p*-values denotes statistical significance.
* *Source*: 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OR, odds ratio; PY, patient year; RA, rheumatoid arthritis; SES, social economic status.
[a] Cox proportional hazard models (1) are adjusted for age and sex.
[b] Cox proportional hazard models (2) are adjusted for age, sex, SES, rural/urban, hospital size, and fracture type.
[c] Cox proportional hazard models (3) are adjusted for age, sex, SES, rural/urban, hospital size, fracture type, and comorbidities influencing risk of death: Charlson (excl. RA), cardiovascular disease, COPD, malignancy, dementia, alcoholism, diabetes, hyperlipidemia, hormonal replacement therapy, and anticoagulants.
[d] The numerator represents the number of in-hospital deaths over the total number of deaths within 5 years.
[e] In-hospital mortality was estimated using logistic regression models, and values represent unadjusted and adjusted ORs.

DISCUSSION

In this population-based study, we found that the incident RA cohort had a 28% higher risk of hip fracture than age-matched and sex-matched controls from the general population. Despite being matched on age, the RA cohort, on average, fractured their hips two years earlier than the matched general controls, indicating a premature risk of hip fractures. The incidence rate of hip fracture observed in our cohort was lower than the pooled incidence rates reported in a systematic review (4.33 [95% CI 2.26–8.27])[2] and lower than the risk ratio reported in another systematic review (risk ratio 1.28 [95% CI 1.20–1.37] vs pooled risk ratio 2.64 [95% CI 2.19–3.17]).[16] Several of the included articles in the systematic reviews were based on prevalent RA samples or in samples with differing characteristics, methods used for case ascertainment, and/or comparison/control groups.

Although the absolute risk of hip fracture increased with age for both groups, the relative risk in RA as compared with the general population decreased with increasing age and was no longer higher in individuals with RA above the age of 80 years. This is likely attributed to the low absolute risk of hip fractures at younger ages in the general population[7] leading to a higher relative risk in younger age groups with RA because of a greater risk attributable to RA. The incidence rates, however, are higher in women than men in both the general population[7] and RA cohorts.[15,38] Our findings are consistent with others,[38,39] showing a higher relative risk of hip fracture in men than in women with RA relative to the general population.

In the general population excess mortality after hip fracture is reported compared with age-matched population norms without fractures[9] and the elevated risk persists for several years after the fracture. Excess mortality has also been reported to be higher in younger age groups[9] and in men compared with women regardless of age.[7,28] Few studies have reported on mortality rates after hip fracture in RA. Studies comparing mortality in RA and control groups after hip fracture using data from Taiwan and Korean national databases reported a higher one-year mortality than control groups.[14,15] Similar to our RA cohort findings (19.2%), Gundel et al reported 90-day mortality (17.1%; 95% CI 15.7–18.5) post hip fracture in a large Danish cohort with rheumatic diseases.[40] We observed no significant differences in mortality risk post fracture between RA and general population controls who sustained a hip fracture. Although a slightly lower mortality risk within 90 days of fracture was observed in our RA sample (aHR [95% CI] 0.80 [0.65–0.98]), the clinical significance of this finding is unclear given the small magnitude of the effect, the lack of biologically plausible explanation, and the borderline statistical significance. This finding did not change when analyses were adjusted for comorbidities associated with mortality risk measured at the time of fracture, thus reducing the likelihood of a selection bias, such as a collider stratification bias, because of the sample for postfracture mortality analyses being selected based on the presence of hip fracture, but the possibility of this bias still remains.[41] Other considerations regarding differences between our results and those reported in the literature include well-recognized heterogeneity, with large geographic and ethnic variations in fracture incidence estimates and mortality post hip fracture.[42] Also of note, a comparable percentage of patients both groups received nonoperative treatment which is, in general, indicative of a poor prognosis.[43]

Because RA is a known independent risk factor for fragility fractures,[1] our findings of increased risk for hip fracture were not unexpected. The underlying reasons for increased risk for fractures with RA are likely multifaceted. Chronic inflammation and the use of glucocorticoids have known negative effects on bone mass. Other recognized risk factors for fragility fractures in RA include sex (female), older age, inactivity, lower body mass index, and health behaviors such as smoking, which is more prevalent in RA.[44] Disease-related impairments also place people with RA at a higher risk of falls, which is an important risk factor for hip fracture. People with RA have several intrinsic and extrinsic risk factors for falls.[45] A systematic review reported that the incidence of falls with RA ranged from 10% to 50% over 6 to 12 months periods and were independently associated with age, sex, and disease duration.[45] Given the public health burden of hip fracture especially with older age, fall prevention programs have traditionally targeted older adults. Insofar as adults with RA are at high risk of falling and increase risk of fragility fractures including hip fracture, prevention programs targeting RA have been advocated within the literature.[45,46]

The strengths of this study include the population-based nature of the cohort within a universal health care system, ensuring capture of all fracture events, and representativeness of the sample, including the full spectrum of RA disease severity and age groups. The use of an incident cohort of RA avoided immortal time bias when estimating fracture risk by ensuring all fracture events, including those leading to mortality, were captured. The large sample and long follow-up time allowed sufficient power and time to provide an accurate estimate of fracture rates and of mortality post fracture. Another strength was that the availability of general population controls matched on age, sex, and index RA year, which allowed comparable controls for estimating comparison of fracture risk.

Despite the strengths, some limitations are inherent to administrative data studies, including a degree of uncertainty regarding the RA diagnosis and lack of information on disease activity. We used criteria that had been validated in a subsample who participated in a RA survey, using opinion of an independent rheumatologist reviewing medical records from their treating physicians as gold standard, where the PPV was 0.82.[18] We conducted sensitivity analyses on an RA subsample who received DMARDs, and results did not substantially differ from the main analyses. Notwithstanding, the inclusion of non-RA cases in the sample would bias the results toward the null. Because the onset of RA in this cohort was identified using administrative data, a lag time between the actual symptom onset and diagnosis may exist. The possibility of initial misdiagnosis, with some patients having

another initial musculoskeletal diagnosis, cannot be excluded. Limitations relative to the hip fracture outcomes evaluated in this study include the fact that we were only able to evaluate the type of fracture and fixation, and no other information regarding the surgery and postoperative complications were available. Finally, only all-cause mortality was examined because of the relatively low number of events leading to insufficient power to accurately evaluate differences in cause-specific mortality.

The findings have important clinical implications for the management of RA. Determining the incidence of and mortality rates post hip fractures in RA relative to the general population is an initial step necessary for future initiatives targeting the prevention of hip fractures in RA. Hip fracture in this patient population likely leads to further functional limitations in a patient population already at risk of disability from their arthritis. This also has potentially important socioeconomic ramifications and subsequent consequences on health-related quality of life. Given the sparce evidence on recovery after hip fracture in RA populations, further prospective studies are warranted to determine whether the long-term recovery after a hip fracture in RA differs from the reported recovery in the general population.

In conclusion, the risk of hip fracture in our RA incident cohort was 28% greater than age-matched and sex-matched controls from the general population. Individuals with RA were more likely to fracture at an earlier age; however, after adjustment, the risk of mortality post hip fracture was comparable with the controls, except for an unexpected slightly lower 90-day mortality risk in RA relative to controls, a finding of unclear clinical significance. Although not specifically evaluated in this study, significant burden is usually seen post hip fracture with long recovery periods and commonly a lack of return to the prefracture functional level. From clinical and health policy perspectives, fall prevention interventions specific to RA populations, along with prevention programs addressing osteoporosis risk factors and facilitating early detection and management of osteoporosis, are needed to prevent hip fractures in RA.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Lacaille confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Access to data provided by the Data Stewards is subject to approval but can be requested for research projects through the Data Stewards or their designated service providers. The following data sets were used in this study: BC Cancer, Consolidation, Hospital Separations, Income Band, Lifelabs, Medical Services Plan, Pharmacare, Pharmanet, Vital Statistics-Death. You can find further information regarding these data sets by visiting the PopData project webpage at: https://my.popdata.bc.ca/project_listings/14-131/1985/01/01 - 2018/12/31. All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not reflect the opinions or policies of the Data Steward(s).

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