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Frailty and risk of osteoporotic fractures in patients with rheumatoid arthritis: Data from the Ontario Biologics Research Initiative

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ABSTRACT

The evidence assessing the relationship between frailty and risk of adverse health outcomes in patients with rheumatoid arthritis (RA) remains limited and sparse in the literature. Data from the Ontario Best Practices Research Initiative (OBRI), a clinical registry of patients with RA, were used to explore the relationship between frailty and fracture risk in patients with RA. Patients were referred to OBRI by their participating rheumatologist, and contacted by OBRI trained interviewers. Primary outcome was time to first incident osteoporotic fractures during follow-up that led to a hospitalization or emergency room visit. Frailty was measured by a Rockwood-type frailty index (FI) of deficit accumulation that consisted of 32 health-related deficits. To quantify the relationship between frailty and risk of fracture, we used Cox proportional hazards models with hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) reported. We included 2923 patients (mean age 57.7 standard deviation [SD]: 12.7; 78% female,) for analyses. During a mean follow-up of 3.7 years, there were 125 (4.3%) incident fractures reported. The FI was significantly higher in patients with a fracture compared to controls (0.24 vs. 0.20, $p = 0.02$). The FI was found to be significantly related to increased risk of fracture in the fully-adjusted models, with a HR of 1.04 (95% CI: 1.02–1.06, $p < 0.001$) and 1.58 (95% CI: 1.32–1.89, $p < 0.001$) for per-0.01 and per-SD increase in the FI respectively. In summary, our study demonstrates that higher frailty status is significantly related to increased risk of osteoporotic fractures in patients with RA. Quantifying the frailty status as a research tool may aid in fracture risk assessment, management and decision-making in RA.

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic and progressive inflammatory polyarthritis [1]. Patients with RA are at high risk of skeletal bone loss and increased risk of osteoporotic fractures, due to multiple-factors including chronic inflammation, use of glucocorticoids, and reduced mobility [2]. Screening and evaluating fracture risk in patients with RA may therefore aid in management, intervention and decision-making to reduce their risk of fractures.

Abbreviation: BMD, bone mineral density; *BMI*, body mass index; *CI*, confidence interval; *DAS*, disease activity scores; *ER*, emergency room; *FI*, frailty index; *FRAX*, Fracture Risk Assessment Tool; *HR*, hazard ratio; *MOF*, major osteoporotic fracture; *OBRI*, Ontario Best Practices Research Initiative; *OR*, odds ratio; *RA*, rheumatoid arthritis; *SD*, standard deviation; *TBS*, trabecular bone scores; *VIF*, variance inflation factor

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Frailty is defined as a dynamic condition of increased vulnerability that limits one's social, psychological, and physical functioning [3]. It is recognized that, the frailer a patient is, the greater the likelihood that he/she will develop a future adverse health outcome [4]. Therefore, measuring the degree of frailty can help screen, quantify and predict future risk of adverse health outcomes at a clinical research level and at a healthcare policy level [5]. However, the evidence assessing the relationship between frailty and risk of adverse health outcomes in RA patients remains limited and sparse in the literature. In this study based on data from the Ontario Best Practices Research Initiative (OBRI), we aimed to assess the relationship between frailty and risk of osteoporotic fractures in patients with RA. Our hypotheses included that 1) the patients experiencing an osteoporotic fracture during follow-up had a higher degree of frailty than those without a fracture, and 2) higher frailty was significantly associated with increased risk of fracture.

2. Methods

2.1. Patients and settings

OBRI is a clinical registry of patients with RA in Ontario, Canada (http://www.obri.ca/). OBRI provides a platform for collaboration between rheumatologists, patients and researchers, aiming to improve management and treatment of RA patients [6]. To be included in OBRI, patients had to have active RA, be able to provide informed consent, be seeing a rheumatologist and receiving anti-rheumatic medications. Patients were referred to OBRI by their participating rheumatologist, and contacted by OBRI trained interviewers. Data were collected from the participating rheumatologists every 6 months, and from OBRI interviewers every 3 months in the first two years and every 6 months afterwards. The data collected from rheumatologists included RA disease activity scores, co-morbidity, medication use, and adverse health events. The data collected by OBRI interviewers included patients' demographics, disease history, medication use, co-morbidities, functional outcomes, quality of life, work productivity, and serious side effects. In this analysis, we included the enrolled patients who completed at least 2 visits from January 2010 to December 2016.

2.2. Outcomes

All the outcomes were reported from the patient interviews by OBRI interviewers and checked by using physician reports as references. The primary outcome was time to first incident osteoporotic fractures during follow-up that led to a hospitalization or emergency room (ER) visit, where an osteoporotic fracture was defined as a fracture resulting from the force of a fall from a standing height or less including fractures of the spine, wrist, forearm, ribs, elbow, and other sites (but excluding fractures of fingers, face and toes) [7]. We also used physician reports to examine the fracture dates and ensure no inclusion of traumatic fractures. Our secondary outcome was all-cause hospitalizations during follow-up. No outcome validation from chart reviews or medical records was available in this study.

2.3. Frailty measures and other variables

In this study, we used a Rockwood-type frailty index (FI) of deficit accumulation to measure frailty degree in RA patients [8]. We strictly followed the recommendations for FI development during the construction procedures of our FI [9]. The FI consisted of 32 health-related deficits including activities of daily living (n = 9), co-morbidities (n = 17), and physical signs and symptoms (n = 6). Each deficit was coded as a dichotomized variable ('yes' or 'no') or polychotomized variable to score equal points to map the interval 0–1, which yielded the coding being represented as the frequency or severity of the corresponding deficit included in the FI [9]. Details on the deficits and their coding can be found in Table 1. To calculate the FI for an individual RA patient, all the values of his/her deficits were summed up and divided by the total number of deficits (n = 32). The FI ranged from 0 to 1, with a higher FI indicating greater frailty [10].

Other variables collected from OBRI interviewers included patients' sex, age, body mass index (BMI), smoking, alcohol drinking, use of osteoporosis medications, family history of RA, and duration of RA. Disease Activity Scores (DAS28) were collected from rheumatologist assessment forms.

2.4. Statistical analyses

We described continuous variables using means and standard deviations (SDs), and categorical variables using frequencies and percentages, respectively. We compared patients' baseline variables stratified by patients with and without an incident fracture during follow-up. The crude comparisons were made using Student's *t*-test for continuous variables and Chi-square tests for the categorical variables, respectively. Kaplan-Meier survival function was used to graph the survival curve for risk of osteoporotic fractures during follow-up.

We also used multivariable linear regression analysis to compare FIs between patients with and without a fracture, after adjusting for the variables listed in Table 2 and those that had a variance inflation factor (VIF) < 4 (to avoid the effect of multicollinearity) [11]. To quantify the relationship between frailty and risk of osteoporotic fracture, we used Cox proportional hazards models with hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) reported. Results were shown in both the age-adjusted models and the fully-adjusted models, in which the fully-adjusted models were adjusted for age, sex, BMI, smoking, alcohol drinking, family history of RA, use of osteoporosis medications, DAS28, and duration of RA. We reported results according to both per-0.01 and per-SD increase in the FI.

Regarding the secondary outcome of all-cause hospitalizations, we used logistic regression to assess their relationship with FI because no data on the dates of hospitalizations were available. We presented their relationship using odds ratios (ORs) and 95% CIs. Results were reported in both the age-adjusted models and the fully-adjusted models, where the fully-adjusted models were adjusted for age, sex, BMI, smoking, alcohol drinking, family history of RA, use of osteoporosis medications, DAS28, and duration of RA.

A predefined subgroup analysis was performed by sex (females vs. males). Another two post-hoc subgroup analyses were also conducted by 1) duration of RA, where the mean of all the patients was used to dichotomize them into long-duration (i.e., > 8.3 years) and short-duration group (i.e., ≤ 8.3 years), and 2) disease activity, where the patients were grouped as either low (DAS28 ≤ 3.2), moderate ($3.2 <$ DAS28 ≤ 5.1), or high (DAS28 > 5.1) [12]. We ran a sensitivity analysis by using a multiple imputation technique to impute missing data, if the data were missing $\geq 10\%$ [13]. All tests were two-sided using the significance level of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

2.5. Ethical approval

This study was conducted according to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all the participants. The University Health Network Research Ethics Board approved the study (REB no. 07-0729 AE).

3. Results

There were 3153 patients who were eligible and participated in enrolment visits. After excluding those who did not complete at least two visits (n = 230), 2923 patients (78% female) with a mean age of 57.7 years (SD: 12.7) were included for analyses. Patients' mean FI at baseline was 0.20 (SD: 0.12), and the age-invariant 99% upper limit was 0.52. During a mean follow-up of 3.7 years (SD: 1.9), there were

Table 1
Deficits included in the frailty index and their coding.

Deficit variables	Coding
Co-morbidities (n = *17*)	
Taking five or more medications[a]	Yes = 1; No = 0
Heart disease	Yes = 1; No = 0
Hypertension	Yes = 1; No = 0
Lung disease	Yes = 1; No = 0
Diabetes	Yes = 1; No = 0
Ulcer or stomach disease	Yes = 1; No = 0
Renal disease	Yes = 1; No = 0
Anemia or other blood disease	Yes = 1; No = 0
Cancer	Yes = 1; No = 0
Depression	Yes = 1; No = 0
Osteo or degenerative arthritis	Yes = 1; No = 0
Psoriasis	Yes = 1; No = 0
Back pain	Yes = 1; No = 0
Liver disease	Yes = 1; No = 0
Tuberculosis	Yes = 1; No = 0
Central nervous system disease	Yes = 1; No = 0
Autoimmune disease	Yes = 1; No = 0
Physical symptoms and signs (n = *6*)	
Unusual fatigue/tiredness in last week	Ten levels causing from 'major problem' to 'no problem'; gradient coding with response of 'major problem' coding as 1 and response of 'no problem' coding as 0
Sleep problem in last week	Ten levels causing from 'major problem' to 'no problem'; gradient coding with response of 'major problem' coding as 1 and response of 'no problem' coding as 0
Problem of mobility	Severe problem = 1; some problem = 0.5; no problem = 0
Problem of self-care	Severe problem = 1; some problem = 0.5; no problem = 0
Problem of usual activities	Severe problem = 1; some problem = 0.5; no problem = 0
Pain or discomfort	Extreme pain or discomfort = 1; moderate pain or discomfort = 0.5; no pain or discomfort = 0
Activities of daily living (n = *9*)	
Difficulty in dressing yourself	Unable = 1; much difficulty = 0.67; some difficulty = 0.33; no difficulty = 0
Difficulty in standing up from an armless chair	Unable = 1; much difficulty = 0.67; some difficulty = 0.33; no difficulty = 0
Difficulty in cutting meat	Unable = 1; much difficulty = 0.67; some difficulty = 0.33; no difficulty = 0
Difficulty in walking outdoors	Unable = 1; much difficulty = 0.67; some difficulty = 0.33; no difficulty = 0
Usually need help with eating	Yes = 1; No = 0
Difficulty in washing and drying your body	Unable = 1; much difficulty = 0.67; some difficulty = 0.33; no difficulty = 0
Difficulty in reaching and getting down a 5-pound object from above your head	Unable = 1; much difficulty = 0.67; some difficulty = 0.33; no difficulty = 0
Difficulty in running errands and shopping	Unable = 1; much difficulty = 0.67; some difficulty = 0.33; no difficulty = 0
Usually need help with hygiene	Yes = 1; No = 0

[a] This deficit included all medications except for osteoporosis medications.

Table 2
Comparison of baseline characteristics between RA patients with an osteoporotic fracture leading to hospitalization or ER visit and patients without fractures during follow-up.

Baseline characteristics	Incident fracture that led to a hospitalization or ER visit		
	Yes (n = 125)	No (n = 2798)	p-Value
Age: mean (SD), years	62.2 (11.7)	57.5 (12.7)	< 0.001
Female: n (%)	109 (87%)	2181 (78%)	0.014
RA duration: mean (SD), years	11.5 (11.3)	8.3 (9.7)	0.003
DAS28: mean (SD)	4.5 (1.6)	4.3 (1.6)	0.29
BMI: mean (SD), kg/m^2	26.8 (5.8)	27.2 (5.8)	0.47
Family history of RA: n (%)	34 (29%)	770 (28%)	0.89
Smoking: n (%)	6 (5%)	387 (14%)	0.004
Alcohol drinking: n (%)	13 (10%)	692 (25%)	< 0.001
Osteoporosis medication use: n (%)	48 (38%)	773 (28%)	0.009
FI: mean (SD)	0.24 (0.12)	0.20 (0.12)	0.024

ER = emergency room; SD = standard deviation; RA = rheumatoid arthritis; BMI = body mass index; DAS = disease activity score; FI = frailty index;

125 (4.3%) incident osteoporotic fractures reported including 21 forearm or wrist fractures, 10 spine, 12 hip, 8 shoulder, 16 ankle, 13 ft, 11 rib, 7 femur, 6 elbow, 4 pelvis and 17 other fractures. Fig. 1 displays the Kaplan-Meier survival curve for the risk of incident fractures. As shown in Table 2, patients experiencing a fracture were older, more likely to be females, had a longer RA duration, and more likely to take osteoporosis medications, compared to patients without a fracture. However, patients with a fracture were less likely to smoke or consume alcohol. The FI was significantly higher in patients with a fracture compared to controls (0.24 vs. 0.20, p = 0.02). Results from multivariable linear regression analysis also showed that the difference in FI between patients with a fracture and controls was statistically significant: mean difference = 0.02, p = 0.03.

Table 3 displays the relationship between the FI and risk of osteoporotic fractures and hospitalization. The FI was found to be significantly related to increased risk of fracture in the fully-adjusted models, with a HR of 1.04 (95% CI: 1.02–1.05, p < 0.001) and 1.58 (95% CI: 1.32–1.89, p < 0.001) for per-0.01 and per-SD increase in the FI respectively. There were 724 (24.8%) all-cause hospitalizations documented during follow-up. A significant relationship was also observed between the FI and risk of hospitalizations in the fully-adjusted models: OR = 1.03 (95% CI: 1.02–1.04, p < 0.001) for per-0.01 increase and OR = 1.43 (95% CI: 1.30–1.58, p < 0.001) for per-SD increase in the FI. All the age-adjusted models yielded similar findings to those from fully-adjusted models.

As shown in Table 4, the FI was significantly related to increased risk of fractures when subgroup analyses were performed by sex: HR = 1.07 and 2.33 (p = 0.007) for per-0.01 and per-SD FI increase in males, and HR = 1.03 and 1.53 (p < 0.001) for per-0.01 and per-SD increase in females, respectively. Significant relationship between the FI and risk of fractures was also observed in subgroup analyses by duration of RA and disease activity (Table 4). No significant subgroup

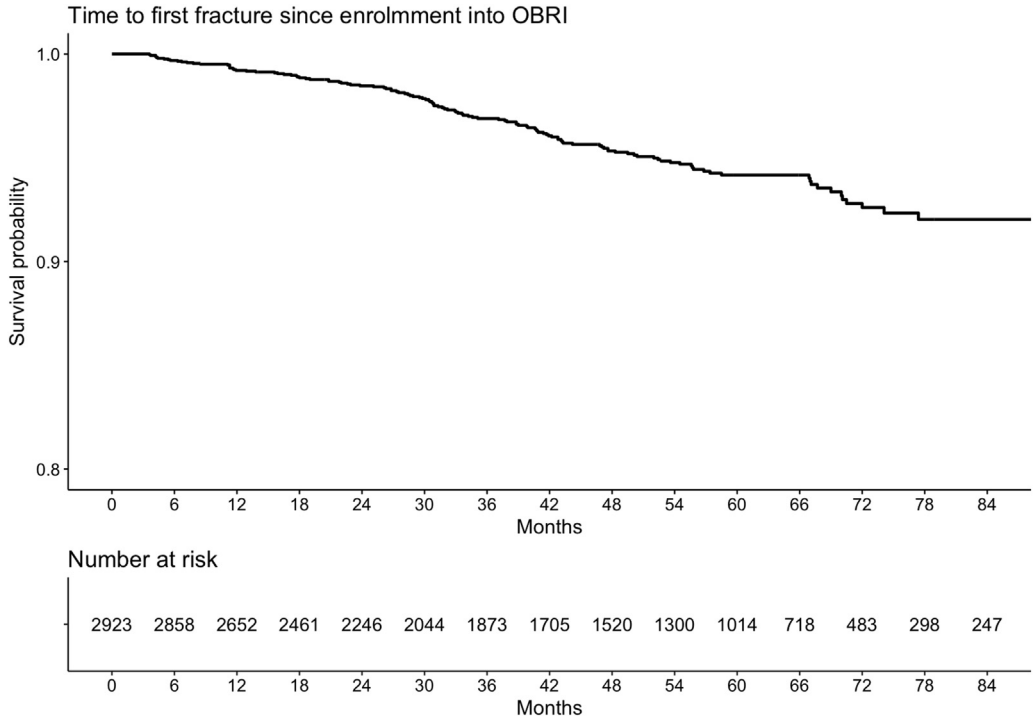

Fig. 1. Kaplan-Meier survival curve for risk of incident osteoporotic fractures.

Table 3
Relationship between baseline frailty index and risk of incident osteoporotic fractures and all-cause hospitalization during follow-up.

Outcome	Per-0.01 increase in FI		Per-SD increase in FI	
	Statistics[a]	p-Value	Statistics[a]	p-Value
Incident fracture that led to a hospitalization or ER visit (n = 125, 4.3%)				
Age-adjusted model	1.04 (1.03–1.05)	< 0.001	1.60 (1.39–1.84)	< 0.001
Fully-adjusted model[b]	1.04 (1.02–1.06)	< 0.001	1.58 (1.32–1.89)	< 0.001
All-cause hospitalization (n = 724, 24.8%)				
Age-adjusted model	1.03 (1.02–1.04)	< 0.001	1.44 (1.33–1.57)	< 0.001
Fully-adjusted model[b]	1.03 (1.02–1.04)	< 0.001	1.43 (1.30–1.58)	< 0.001

FI = frailty index; ER = emergency room.
[a] Results expressed as hazard ratios (HRs) and 95% confidence intervals for outcome of incident fractures, and odds ratios (ORs) and 95% confidence intervals for outcome of all-cause hospitalization
[b] Model adjusted for age, sex, BMI, smoking, alcohol drinking, family history of RA, use of osteoporosis medications, DAS28, and duration of RA.

differences were found in all the three subgroups (all p-values > 0.05). Findings from the sensitivity analysis by using twenty multiple imputations for missing data showed similar results to those from main analyses (Table 4).

4. Discussion

Based on the data from patients with RA, we found the participants experiencing an osteoporotic fracture were significantly frailer than their controls. We also observed that higher frailty status was significantly related to increased risk of fractures and hospitalizations. Results from subgroup and sensitivity analyses corroborated the robustness of the main findings.

Patients with RA were at high risk of osteoporotic fracture. For example, data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort reported that the 3-year incident rate of osteoporotic fracture was 2.7% (n = 81) in the 3010 Canadian

Table 4
Results of subgroup and sensitivity analyses in fully-adjusted models for relationship between frailty index and risk of incident osteoporotic fractures.

Analyses	Incident fracture that led to a hospitalization or ER visit (n = 125)		
	Per-0.01 increase in FI[a]	Per-SD increase in FI[a]	p-Value
Subgroup analysis			
Sex[b]			
Males	1.07 (1.02–1.11)	2.33 (1.26–4.30)	0.007
Females	1.03 (1.02–1.05)	1.53 (1.27–1.85)	< 0.001
Duration of RA[c]			
Short	1.05 (1.03–1.07)	1.75 (1.36–2.23)	< 0.001
Long	1.04 (1.01–1.06)	1.49 (1.14–1.95)	< 0.001
Disease activity[d]			
Low	1.07 (1.04–1.11)	2.24 (1.52–3.30)	< 0.001
Moderate	1.04 (1.01–1.06)	1.51 (1.15–1.98)	0.002
High	1.06 (1.02–1.11)	2.01 (1.25–3.24)	0.003
Sensitivity analysis			
Using multiple imputations[e]	1.04 (1.03–1.05)	1.41 (1.19–1.66)	< 0.001

FI = frailty index; ER = emergency room.
[a] Results expressed as hazard ratios (HRs) and 95% confidence intervals;
[b] There were 16 fractures (2.2%) observed in males and 109 fractures (5.0%) in females; model adjusted for age, BMI, smoking, alcohol drinking, family history of RA, use of osteoporosis medications, DAS28, and duration of RA.
[c] There were 61 fractures (3.3%) observed in short-duration and 64 fractures (6.0%) in long-duration group; model adjusted for age, BMI, smoking, alcohol drinking, family history of RA, use of osteoporosis medications, and DAS28.
[d] There were 25 fractures (4.1%) observed in low, 45 (4.3%) in moderate, and 37 (4.5%) in high disease activity group; model adjusted for age, BMI, smoking, alcohol drinking, family history of RA, use of osteoporosis medications, and duration of RA.
[e] Twenty multiple imputations used for imputing missing data; model adjusted for age, sex, BMI, smoking, alcohol drinking, family history of RA, use of osteoporosis medications, DAS28, and duration of RA.

participants who had a mean age of 69 years and did not have a diagnosis of RA [14,15]. Compared with these participants without RA, our study revealed a significantly higher fracture incidence rate (4.3%, n = 125) in the patients with RA (p = 0.001). Our results confirmed the frailty concept in patients with RA that the higher a participant's FI, indicated as being frailer, the higher his/her risk of adverse health outcomes. Thus, frailty status measures were significantly associated with risk of osteoporotic fractures and hospitalizations (Table 3). Frailty is a deteriorating health condition with aging; however, presence of chronic diseases such as RA can accelerate the frailty process [5]. In our study, after accounting for the effect of chronological age, the frailty status could serve as an estimator of true biological age [16] to quantify the fracture risk in RA. Even though each individual deficit may not contribute to the increased fracture risk, the deficit accumulation could lead to an elevated frailty degree that increased one's vulnerability to adverse outcomes [17]. Assessing the frailty status, when feasible and appropriate, could better discriminate those at high risk of osteoporotic fracture from the general RA population regardless of their chronological ages, which could therefore help with risk evaluation, risk management, and decision-making especially in the primary and community settings.

Although the evidence remains sparse in the literature, there is some research work investigating frailty and risk of adverse outcomes in patients with RA. For instance, data from a US cohort study (n = 124) showed that frailty measurement was significantly related with decreased physical function in participants with RA [18]. Another ongoing study conducted in Japan included 95 participants with RA and reported that frailty was significantly related with increased disease activity and reduced physical function [19]. There was one Spanish study reporting that the prevalence of frailty in patients with RA was unexpectedly high (23%); however, they did not evaluate whether frailty was related with risk of adverse outcomes [20]. Unfortunately, none of them explored the relationship between frailty and osteoporotic fracture risk. Although similarities existed between participants with RA and the general populations with osteoporosis regarding their fracture risk, RA itself was a well-known risk factor for increased osteoporotic fractures, mainly due to disease activity and the use of glucocorticoids [21]. The FRAX (Fracture Risk Assessment Tool), a popular risk prediction for the 10-year absolute risk of hip fracture and major osteoporotic fracture (MOF), has incorporated RA in its calculation algorithm. Nevertheless, it received criticism of the algorithm because it did not consider dose of glucocorticoids, disease activity or duration, or related immobility, which thereby limiting its predictive accuracy [2,22]. For instance, the FRAX has been reported to overestimate risk of major osteoporotic fracture and hip fracture in patients with RA in the UK [23]. One study compared predictive powers between FRAX and frailty for risk of MOF and hip fractures in women aged ≥65 years and at risk of osteoporotic fractures [15]. They reported that FRAX and frailty were comparable in predicting fracture risk. Although there were only 12% of the participants reported to have RA, their findings may provide some insight on improving fracture risk prediction in RA [15]. How to further apply the concept of frailty to assessing fracture risk in RA, and how to use frailty to help enhance predictive accuracy of prediction tools including FRAX, remained worthwhile and interesting endeavours in health research because such investigations would advance fracture risk evaluation, patient management, and healthcare provision.

This study has some strengths. Participants were enrolled from multiple rheumatology clinics across Ontario with very few exclusion criteria, which could enhance population representativeness and generalizability of our findings. We validated the outcome data using physician reports to ensure outcome accuracy. The FI construction was strictly followed the recommended procedure [9], with each health-related deficit selected by authors' discussion and consensus (Table 1). Results were obtained from a large sample size with a follow-up of approximately 4 years, and from vigorous statistical analyses, which may elevate the strength of evidence. Some limitations also existed in the study. We could not fully account for the lurking confounding because data were from an observational study with non-randomized design. No information on radiological imaging such as bone mineral density (BMD) measures or trabecular bone scores (TBS) was available, which prevented us from further clarifying whether frailty was related to osteoporotic fracture risk independent of BMD and TBS. However, despite the lack of BMD or TBS measures, osteoporotic fracture risk could be evaluated using clinical risk factors, which was similar to FRAX without BMD. In addition, we could not explore the impact of mortality as a competing risk for fractures on our findings [24], due to lack of information on mortality and the dates. We defined the primary outcome as incident osteoporotic fractures that led to a hospitalization or ER visit. It may probably leave out some clinically silent fractures such as vertebral fractures [2], thereby underestimating the outcome incidence and impairing the validity of study results. We could not assess the relationship between the FI and fracture risk in specific sites because of their small numbers of fracture events and thus insufficient power and model instability. For instance, the small number of hip fracture (n = 12) precluded us from further investigating the association between frailty and hip fracture risk alone. Furthermore, the FI measures generally required 30 to 40 deficits to be included [9]; this would preclude its application in busy clinical practice, although it could be served as a helpful research tool at a health research level and at a healthcare policy level [25].

In conclusion, our study demonstrates that higher frailty status is significantly related to increased risk of osteoporotic fractures in patients with RA. Quantifying the frailty status as a research tool may aid in fracture risk assessment, management and decision-making in RA.

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All other authors have declared no conflicts of interest.

Contributors

All authors contributed to the study conception. GL and JT drafted the first version of manuscript, and incorporated comments from other authors for revisions. All authors read and approved the final version of the manuscript.

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