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ORIGINAL ARTICLE

The association between 10-year fracture risk by FRAX and osteoporotic fractures with disease activity in patients with rheumatoid arthritis

Ratanapha Phuan-udom [1,2] · Nittaya Lektrakul [3] · Wanruchada Katchamart [1]

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Abstract

As rheumatoid arthritis (RA) is an independent risk factor for osteoporotic fractures, the severity of disease activity may correlate with fracture risk. Our objectives were to determine the prevalence of major osteoporotic and hip fractures in patients with RA and to identify the factors related to their 10-year probabilities. This study enrolled 232 patients with RA, aged 40–90 years, who participated in the Siriraj RA Cohort in 2016 and 2017. Demographic data, disease activity scores 28 (DAS28), and health assessment questionnaires (HAQ) were collected. All participants were evaluated for asymptomatic vertebral fractures by thoracolumbar spine radiography. The osteoporotic fracture risks were determined using the fracture risk assessment tool (FRAX). Most subjects were postmenopausal women in their sixth decade; the median disease duration was 12.95 years. Forty-six percent of patients had osteoporotic fractures, and most (87%) were vertebral fractures. Eighty-one patients had asymptomatic vertebral compression fractures. Of those, 57%, 25%, and 18% had low, moderate, and high 10-year probabilities of major osteoporotic fractures, respectively, while 51%, 34%, and 15% had low, moderate, and high 10-year probabilities of hip fractures, respectively. Factors significantly associated with the 10-year probabilities of major osteoporotic and hip fractures were disease duration (p 0.017, 0.009), menopause duration ($p < 0.001$ both), cumulative disease activity (DAS28; p 0.004, 0.029), and cumulative functional disability (HAQ; $p < 0.001$ both). Moderate to high 10-year probabilities of major osteoporotic and hip fractures are common in RA. Cumulative disease severity is a high risk for osteoporotic fractures.

Keywords 10-year probability of fracture · Fracture risk assessment · FRAX · Osteoporosis · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease presenting with polyarthritis and extra-articular manifestations. The prevalence of RA is 0.5–1.5% in the USA [1–3] and 0.12% in Thailand [4]. Patients with RA usually have other co-morbid diseases, which affect their survival [5–7]. One of the most important co-morbid diseases is osteoporosis, characterized by low bone mass, a microarchitecture deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk [8]. The World Health Organization has established a threshold value for the presence of osteoporosis. The disease is diagnosed when the value of an individual's bone mineral density, or bone mineral content, is equal to, or more than, 2.5 standard deviations (SD) below the young adult mean value [9].

There are multiple causes of osteoporosis, including advanced age, menopause, malnutrition, a low dietary intake of calcium, vitamin D deficiency, excess alcohol consumption, heavy smoking, glucocorticoid use, and immobilization. Furthermore, endocrine disorders and chronic inflammatory diseases, such as hyperthyroidism, RA, and systemic lupus erythematosus, are demonstrated risk factors for osteoporosis.

The incidence of osteoporosis among RA patients is double than that for the general population [10]. In addition, their incidence rate of fractures is 1.5 times higher than that for the normal population [11].

Multiple factors contribute to bone loss in patients with RA. The chronic inflammatory condition of RA involves the

✉ Wanruchada Katchamart
wanruchada.kat@mahidol.ac.th; wanda.katchamart@gmail.com

[1] Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Asadang Building 8th Floor, Bangkoknoi, Bangkok 10700, Thailand

[2] Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

[3] Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

pathological mechanisms of both local and systemic bone loss. Various cytokines, such as tumor necrotic factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-17 (IL-17), increase bone resorption activity by activation of osteoclasts [12–15], resulting in a reduced bone mineral density. Glucocorticoids are commonly used for RA treatment. They suppress bone formation, increase bone resorption, decrease intestinal calcium absorption, and reduce renal calcium reabsorption [16]. Moreover, patients with RA usually limit their normal activities due to pain, joint deformities, and appetite loss, leading to calcium and vitamin D insufficiencies.

Dual-energy X-ray absorptiometry (DXA) is the gold standard for osteoporosis evaluation; unfortunately, DXA is not widely available globally because the equipment needed is expensive and requires a well-trained operator. Consequently, the fracture risk assessment tool, or FRAX, was developed to assist clinicians with predicting the probability of fractures.

The 10-year probability of an osteoporotic fracture can be evaluated by FRAX, an inexpensive, reliable, and validated tool [17–19]. It is widely used in many countries around the world, including Thailand, and its assessment is based on the clinical risk factors of age, sex, body mass index (BMI), history of fragility fracture, history of parental hip fracture, smoking, alcohol consumption, oral glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and bone mineral density of the hip [17, 20].

As mentioned above, patients with RA have several factors, which lead to bone loss. Therefore, by using the FRAX tool in patients with RA, the objectives of this study were to determine the prevalence of major osteoporotic and hip fractures and to identify the factors related to their 10-year probabilities.

Materials and methods

Patients eligible to participate in this study were diagnosed with RA using either the American College of Rheumatology (ACR) 1987 or ACR/European League Against Rheumatism (EULAR) 2010 criteria; were aged 40–90 years; and participated in the concurrent study Siriraj Rheumatoid Arthritis Cohort at Siriraj Hospital in 2016 and 2017. Those patients who had less than two visits of follow-up were excluded.

For the present study, clinical data were collected from May 2016 to January 2017. A total of 232 included patients gave their written informed consent. The demographic data comprised age, sex, body weight, height, underlying disease, smoking and alcohol consumption status, and menopausal status. The clinical disease activity of RA and the functional status were assessed using the disease activity score 28 (DAS28) and the health assessment questionnaire (HAQ). Treatments, which included glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), calcium and/or vitamin D supplements, and antiresorptive drugs, were reviewed. In addition, data on the clinical risk factors needed for the FRAX tool were collected.

An osteoporotic fragility fracture is defined as any fracture site that results from a minimal trauma (i.e., with a force equivalent to a fall from a standing height or less) or from no identifiable trauma [21]. Plain radiography of the thoracolumbar spine was performed on all patients in our study because some may have had asymptomatic vertebral fractures. The diagnostic criterion for a vertebral compression fracture was defined as a difference between the anterior and posterior vertebral height of greater than 4 mm, as revealed in a lateral thoracolumbar spine radiograph [22]. If more than one fracture site or more than one level of vertebrae was involved, multiple-site fractures were described. In this study, the musculoskeletal radiologist (NL) interpreted all radiographs of the thoracolumbar spine in a blinded manner.

We used DAS28 and HAQ to describe the disease activity of RA. DAS28, a reliable [23] and validated tool [24, 25], is a composite measure which is based on the tender joint count, swelling joint count, erythrocyte sedimentation rate, and patient assessment of global health. The Thai HAQ, a validated Thai version [26] of HAQ, was used for the functional status assessment. Because of the different time intervals between the visits of each patient, we used time-adjusted means for DAS28 and HAQ to represent the overall previous disease severities for each patient. The time-adjusted means were determined from the area under the curve of the values over time by first adding the areas for each block of visit intervals, and then dividing the total by the length of time for the whole period [27].

The 10-year probabilities of osteoporotic fractures were calculated with the FRAX tool provided at the website http://www.shef.ac.uk/FRAX. The specific clinical risk factors used by the tool were age, sex, weight, height, history of fragility fracture, history of parental hip fracture, current smoking status, consumption of 3 or more units of alcohol daily, oral glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis. The definitions we used for each of those factors were those presented in the instructions for the FRAX tool. A previous fracture was defined as any fragility fracture sustained during adult life which resulted from minimal or unidentifiable trauma, including a morphometric vertebral fracture. A unit of alcohol was defined as 8–10 g of alcohol, which is equivalent to 285 ml of beer, 120 ml of wine, 60 ml of aperitif, or 30 ml of spirits. A parental hip fracture was defined as a history of a maternal or paternal hip fracture. Glucocorticoid use was defined as either the current use of oral glucocorticoids or a previous use of oral glucocorticoids lasting more than 3 months, and at a dose of

5 mg or more of prednisolone daily or the equivalent dosage of other glucocorticoids. Secondary osteoporosis was assumed if the patient had a disorder that is strongly associated with osteoporosis, namely, type I diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism, premature menopause (< 45 years), chronic malnutrition, malabsorption, and chronic liver disease.

The FRAX tool provides two results. The first is a prediction of the 10-year risk for a hip fracture, and the other is a prediction of the 10-year risk for a major osteoporotic fracture of the hip, spine, forearm, or humerus. In this study, we estimated the 10-year probabilities of fractures without a bone mineral density (BMD) value. The probabilities were categorized as low, moderate, or high. A low 10-year probability had a value of less than 10 for a major osteoporotic fracture or less than 3 for a hip fracture. A high 10-year probability had a value of greater than 20 for a major osteoporotic fracture or greater than 10 for a hip fracture. A moderate 10-year probability had a value between those specified for the low and high probability groups.

Statistical analyses

A descriptive analysis was performed using the mean and standard deviations (SD) of the quantitative variables with a normal distribution. The median and the interquartile range (IQR) were calculated for those variables with a non-normal distribution. An independent sample *t* test was applied to compare the means of the variables with a normal distribution, and the Mann-Whitney *U* test was used for variables with a non-normal distribution. To compare the quantitative variables between the three probability groups, the Kruskal-Wallis *H* test was used. Either the chi-square test or Fisher's exact test was used for the qualitative variables. A p value of less than 0.05, two-sided, was considered statistically significant. All statistical analyses were conducted with SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to the principles outlined in the Guideline for Good Clinical Practice International Conference on Harmonization (ICH) Tripartite Guideline (January 1997). The study protocol was approved by local ethics committee, the Siriraj institutional review board.

Results

In this study, 232 patients with RA were enrolled from the Siriraj RA Cohort. Their baseline characteristics are at Table 1. The median follow-up time (IQR) was 57 (51–63) months. Their mean age (SD) was 61.6 (9.91) years; most (89%) were female; and the median disease duration (IQR) was 12.95 (8.47–19.75) years. Most of the women (86%) were in the menopausal period, with a median menopause duration (IQR) of 10 (0–18) years and 18% of these being early menopausal (i.e., an onset before age 45). Few patients were current smokers or consumers of alcohol. Almost half of the patients were currently in remission or had a low disease activity. Most of the enrolled patients had a mildly impaired functional status, with a median HAQ (IQR) of 0.50 (0.125–1.25). Most of them were being treated with at least one DMARD, with a median (IQR) of two (2–3); methotrexate was the most commonly used DMARD (82%). Seven percent of patients currently used a biologic agent. Forty percent have used prednisolone at some point, but only 12% were current users. Forty-six percent had an osteoporotic fracture; of these, 92 (87%) were a vertebral fracture, 9 (8.5%) a hip fracture, 7 (6.6%) a wrist fracture, 4 (3.8%) a foot fracture, 3 (2.8%) a lower leg fracture, and 2 (1.89%) a humerus fracture (Fig. 1). In this study, all patients who were diagnosed with an osteoporotic fracture of the foot had a history of minimal trauma. Eighty-one out of the 92 patients (88%) with a vertebral fracture were asymptomatic. All asymptomatic fractures were vertebral fractures. Therefore, almost half of those patients (48%) were multiple-site fracture. In our study population, only 12 patients (5%) had already been diagnosed with osteoporosis and previously treated with an antiresorptive drug.

10-year probability of major osteoporotic fracture

As indicated at Table 2, the FRAX tool determined that 57% (132), 25% (59), and 18% (41) of the enrolled patients had low, moderate, and high 10-year probabilities of having major osteoporotic fractures, respectively. To identify the factors that may be related to the fracture risk, we compared the variables with the FRAX elements for the three groups. Among those three groups, the patients of the high 10-year probability group were the oldest. In addition, all women in high and moderate 10-year probability groups were menopause. The disease duration and duration of menopause were significantly longest in the high 10-year probability group. As for the RA disease severity, the cumulative disease activity and cumulative functional disability were significantly highest in the high-risk group, with a time-adjusted mean DAS28 of 3.31, 3.45, and 3.74, p 0.004, and a time-adjusted mean HAQ of 0.42, 0.68, and 1.33, $p < 0.001$, for the low, moderate, and high 10-year probability groups, respectively. Additionally, the proportion of patients with remission to low disease activity (DAS28 < 3.2) was also significantly lowest in the high probability group, with 78 (59%), 22 (37%), and 12 (29%), p 0.001, for the low, moderate, and high 10-year probability

Table 1 Baseline characteristics of patients

Characteristics	Number of patients ($N = 232$)
Age (years), mean (min–max, SD)	61.6 (40–84, 9.91)
Female (%)	207 (89%)
Body mass index (kg/m^2), mean (SD)	23.85 (4.41)
Underlying disease (%)	
Hypertension	97 (42%)
Diabetes mellitus	16 (7%)
Dyslipidemia	82 (35%)
Osteoporosis	12 (5%)
Menopausal women (%)	177 (86%)
Early menopausal women (%)	32 (15%)
Menopause duration (years), median (IQR)	10 (0–18)
Current alcohol consumption, > 3 units/day (%)	6 (3%)
Current smoker (%)	8 (3%)
Disease duration (years), median (IQR)	12.95 (8.47–19.75)
Rheumatoid factor positivity (%)	163 (70%)
ACPAs positivity (%)	160 (69%)
Current DAS28, mean (SD)	3.45 (1.16)
Current disease remission or low disease activity, DAS28 < 3.2 (%)	112 (48%)
Current HAQ, median (IQR)	0.50 (0.125–1.25)
Calcium supplement (%)	90 (39%)
Vitamin D supplement (%)	78 (34%)
Prednisolone use (%)	92 (40%)
Cumulative prednisolone dose (mg), median (IQR)	1800 (708.75–3429.56)
Daily prednisolone dose (mg), median (IQR)	2.32 (0.88–3.40)
Current DMARDs use number, median (IQR)	2 (2–3)
Methotrexate use (%)	189 (82%)
Methotrexate dose (mg), mean (SD)	11.14 (3.93)
Sulfasalazine use (%)	85 (37%)
Leflunomide use (%)	53 (23%)
Antimalarial drug use (%)	135 (58%)
Azathioprine use (%)	8 (3%)
Cyclosporine A use (%)	5 (2%)
Gold salt use (%)	19 (8%)
Biologic DMARDs (%)	17 (7%)
Anti-tumor necrotic factor (%)	10 (4%)
Other biologic DMARDs (%)	7 (3%)
Regular NSAIDs usage (%)	70 (30%)

SD, standard deviation; *IQR*, interquartile range; *kg*, kilogram; *cm*, centimeter; *kg/m^2* , kilogram per square meters, *DAS28*, disease activity score 28; *HAQ*, health assessment questionnaire; *DMARDs*, disease-modifying antirheumatic drugs; *NSAIDs*, nonsteroidal anti-inflammatory drugs

groups, respectively. There was no significant difference between groups for both the cumulative and daily doses of prednisolone, BMI < 20 kg/m^2, alcohol consumer, smoking, MTX or biologic agent use, and the presence of rheumatoid factor or ACPA. Other clinical factors (BMI, prednisolone usage, previous fracture, multiple-site fracture, and parent fracture hip) were significantly different between groups because they were factors that use for FRAX tool. However, proportion of early menopausal women, a known cause of secondary osteoporosis, was insignificantly difference between groups.

10-year probability of hip fracture

Based on the FRAX tool, 118 (51%), 79 (34%), and 35 (15%) patients had low, moderate, and high 10-year probabilities of

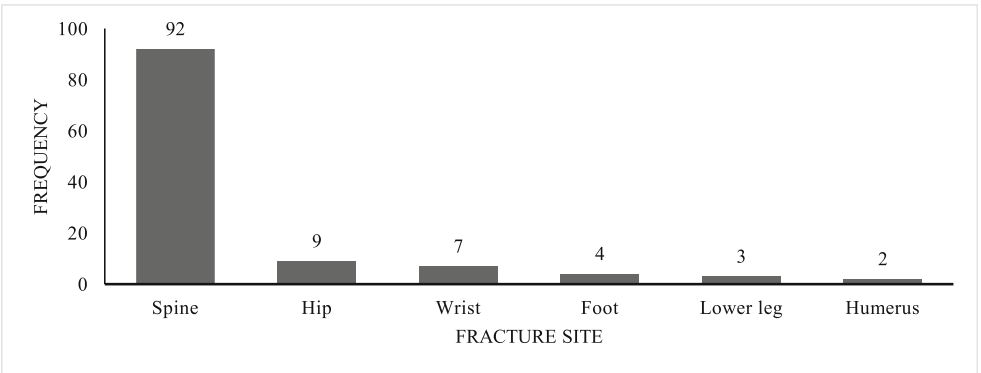

Fig. 1 Frequency of fracture site in 106 enrolled RA patients who had fracture

Table 2 Characteristics of patients in the 10-year probability of major osteoporotic fracture groups

Characteristics	Low (< 10%) $N = 132$	Moderate (10–20%) $N = 59$	High (> 20%) $N = 41$	p value
Age (years), mean (SD)	56.4 (8.0)	66.3 (7.7)	71.7 (6.9)	< 0.001
Female (%)	111 (84%)	55 (93%)	41 (100%)	0.010
Body mass index (kg/m^2), mean (SD)	24.50 (4.64)	23.62 (4.06)	22.05 (3.62)	0.007
Body mass index < 20 kg/m^2 (%)	21 (16%)	11 (19%)	11 (27%)	0.301
Menopausal women (%)	83 (75%)	55 (100%)	41 (100%)	< 0.001
Early menopausal women (%)	15 (14%)	13 (24%)	4 (10%)	0.133
Menopause duration (years), median (IQR)	10 (0–10.8)	15 (8–23)	22.5 (15.5–28)	< 0.001
Alcohol consumer (%)	4 (3%)	2 (3%)	0 (0%)	0.203
Current smoker (%)	6 (5%)	1 (2%)	1 (2%)	0.962
Prednisolone usage (%)	41 (31%)	23 (39%)	25 (61%)	0.003
Cumulative prednisolone dose (mg), median (IQR)	1458 (653.8–3368.3)	2259 (783–3788.8)	1395 (684–3815)	0.681
Daily prednisolone (mg), median (IQR)	2 (1.05–3.28)	2.29 (0.62–3.72)	2.5 (0.73–3.41)	0.997
Methotrexate use (%)	111 (84%)	43 (73%)	36 (88%)	0.097
Biologic DMARDs use (%)	6 (5%)	7 (12%)	5 (12%)	0.105
Previous fracture (%)	32 (24%)	36 (61%)	38 (93%)	< 0.001
Multiple-site fracture, ≥ 2 sites (%)	15 (11%)	20 (34%)	16 (39%)	< 0.001
Parent with fractured hip (%)	6 (5%)	3 (5%)	9 (22%)	0.003
Rheumatoid factor positivity (%)	94 (73%)	38 (68%)	32 (80%)	0.420
ACPAs positivity (%)	92 (77%)	38 (67%)	30 (81%)	0.215
Disease duration (years), median (IQR)	11.7 (7.6–18.6)	13.3 (8.8–18.2)	17 (9.6–23.1)	0.017
Time-adjusted mean DAS28, mean (SD)	3.31 (0.81)	3.45 (0.81)	3.74 (0.68)	0.004
Time-adjusted mean HAQ, median (IQR)	0.42 (0.14–0.89)	0.68 (0.36–1.23)	1.33 (0.63–1.65)	< 0.001
Remission to low disease activity (%)	78 (59%)	22 (37%)	12 (29%)	0.001

SD, standard deviation; *IQR*, interquartile range; *kg*, kilogram; *cm*, centimeter; *kg/m^2*, kilogram per square meters; *DMARDs*, disease-modifying antirheumatic drugs; *ACPA*, anti-citrullinated peptide antibody; *DAS28*, disease activity score 28; *HAQ*, health assessment questionnaire

having hip fractures, respectively (Table 3). With regard to the factors related to the risk of a hip fracture, findings similar to the 10-year probability of having a major osteoporotic fracture were found. The duration of menopause, disease duration, proportion of patients with remission to low disease activity, cumulative disease activity, and functional disability were significantly different between the groups. On the contrary to 10-year probability of major osteoporotic fracture, BMI lower than 20 kg/m^2 was significantly different between groups.

Discussion

In this study, we demonstrated that patients with RA are at high risk for an osteoporotic fracture. Nearly half of the patients in our study had osteoporotic fractures, of which most were asymptomatic vertebral fractures. In addition to the traditional risk factors for osteoporosis, this study demonstrated that RA disease severity may be associated with fracture risk. It has been shown in previous studies that functional impairment is correlated with clinical fracture [28–30]. Patients with a high HAQ score tend to limit their daily activities due to joint pain or deformities, resulting in decreased muscle strength. Moreover, those patients usually limit their weight-bearing activity and sun exposure, leading to low bone quality; they also have a high risk of recurrent falling. Therefore, RA patients who have a poor functional status have a high risk for fracture. As for disease activity, measured by DAS28, the correlation with osteoporotic fractures is still inconclusive. A previous cross-sectional study in Ireland, which explored vertebral fractures by vertebral fracture assessment (VFA) in 603 patients with RA, documented that DAS28 was an independent risk factor for vertebral fracture [31]. On the other hand, some studies have indicated that there was no association between DAS28 and osteoporotic fracture [30, 32].

An observational study was conducted in Japan of 3972 patients with RA; their mean age was 62 years, and most of the subjects were female [33]. It was found that the DAS28 and HAQ scores significantly differed among the three fracture risk groups, as measured by FRAX without BMD. The clinical characteristics of the patients and the results were similar to those of our study. Moreover, a recent published retrospective observational study [34], which aimed to evaluate osteoporotic fracture risk with FRAX tool in Chinese patients with RA,

Table 3 Characteristics of patients in RA cohort in the 10-year probability of hip fracture groups

Characteristics	Low (< 3%) $N = 118$	Moderate (3–10%) $N = 79$	High (> 10%) $N = 35$	p value
Age (years), mean (SD)	55.6 (7.4)	65.2 (7.4)	74.2 (5.9)	< 0.001
Female (%)	103 (87%)	69 (87%)	35 (100%)	0.083
Body mass index (kg/m^2), mean (SD)	25.22 (4.45)	23.13 (4.00)	20.82 (3.19)	< 0.001
Body mass index < 20 kg/m^2 (%)	11 (9%)	19 (24%)	13 (37%)	< 0.001
Menopausal women (%)	75 (64%)	69 (87%)	35 (100%)	< 0.001
Early menopausal women (%)	15 (13%)	13 (17%)	4 (11%)	0.190
Menopause duration (year), median (IQR)	5 (0–12)	12 (6–19)	24 (19–30)	< 0.001
Alcohol consumer (%)	4 (3%)	2 (3%)	0 (0%)	0.340
Current smoker (%)	5 (4%)	3 (4%)	0 (0%)	0.645
Prednisolone usage (%)	36 (31%)	37 (47%)	18 (51%)	< 0.001
Cumulative prednisolone dose (mg), median (IQR)	1458 (756–3139.8)	2349 (859.5–3808.4)	1147.5 (403.1–2434.7)	0.358
Daily prednisolone (mg), median (IQR)	1.9 (1.1–3.1)	2.4 (0.9–4.7)	2.2 (0.5–2.9)	0.573
Previous fracture (%)	28 (24%)	47 (60%)	31 (89%)	< 0.001
Multiple-site fracture (%)	14 (12%)	22 (28%)	15 (43%)	< 0.001
Parental with fractured hip (%)	7 (6%)	6 (8%)	5 (14%)	0.268
Rheumatoid factor positivity (%)	81 (69%)	56 (71%)	26 (74%)	0.972
ACPAs positivity (%)	81 (69%)	54 (68%)	25 (71%)	0.775
Methotrexate use (%)	98 (87%)	59 (75%)	30 (86%)	0.084
Biologic DMARDs use (%)	7 (6%)	8 (10%)	3 (7%)	0.604
Disease duration (years), median (IQR)	12 (8.2–19.2)	11.9 (7.7–17.1)	17.8 (10.1–25.6)	0.009
Time-adjusted mean DAS28, mean (SD)	3.28 (0.77)	3.52 (0.89)	3.68 (0.57)	0.015
Time-adjusted mean HAQ, median (IQR)	0.45 (0.14–1.01)	0.63 (0.26–1.12)	1.41 (0.63–1.77)	< 0.001
Remission to low disease activity (%)	69 (59%)	33 (42%)	10 (29%)	0.003

SD, standard deviation; *IQR*, interquartile range; *kg*, kilogram; *cm*, centimeter; *kg/m^2*, kilogram per square meters; *DMARDs*, disease-modifying antirheumatic drugs; *ACPA*, anti-citrullinated peptide antibody; *DAS28*, disease activity score 28; *HAQ*, health assessment questionnaire

founded that disease duration and DAS28 were important risk factors for major osteoporotic fracture and hip fractures. Their results were also similar to our results and augmented the relationship between RA disease activity and fracture risk.

As previously described, glucocorticoids are important risk factors for bone loss and osteoporotic fracture [12, 16]. The present study revealed no correlation between the dosage of glucocorticoids (both cumulative and mean daily dose) and the 10-year probabilities of major osteoporotic or hip fractures, whereas the result of previous study in Japanese patients with RA [33] showed that daily prednisolone dose seemed to increase along with the higher fracture risk groups. This may be because only 40% of our patients had ever used prednisolone leading to insufficient power to demonstrate this relationship. Moreover, the FRAX tool model does not account dose-dependent effect of glucocorticoids in their model.

According to previous data described by Orsolini et al. [35], anti-citrullinated protein antibody (ACPA) titers have negative correlation with BMD *Z*-score at femoral site, but not at lumbar site. While our study was not found correlation between neither ACPA nor rheumatoid factor with fracture risk because we used FRAX tool without BMD.

In our study, vertebral compression fractures were diagnosed in 81 out of 232 patients (34.9%) with plain radiographs. In a cross-sectional study [36] of 908 postmenopausal women without a previous diagnosis of osteoporosis, VFA images showed that 20% had vertebral compression fractures. In the case of patients with RA, other studies have reported prevalence rates of morphometric vertebral fractures from 14 to 36% [37–39], comparable to the results of our study.

Furthermore, 66–75% of radiographic vertebral fractures are asymptomatic [40]. The incidence of asymptomatic vertebral fractures in our population was higher than that in previous reports. Therefore, vertebral imaging should be considered for all RA patients who have at least a traditional osteoporotic risk factor.

All patients in this analysis were participants in the concurrent Siriraj RA Cohort study, which was launched in 2011. As we had up to 5 years of historical data related to the disease activity and functional status of those patients, we were able to assess their overall cumulative disease activity.

Our study limitation was due to nature of retrospective data that may not accurate, such as the amount of prescribed glucocorticoids might be different from the actual amount that

patient had taken. Furthermore, some of data (such as age of menopause, history of parental fracture) were recalled data.

Because of the differences in the time intervals between the various visits by each patient, we used time-adjusted means of DAS28 and HAQ to represent the overall previous disease severity for each patient. The adjusted values of DAS28 and HAQ obtained by this method provided more accurate data than using the unchanged means of DAS28 and HAQ.

Although low BMD is an important independent risk factor for osteoporotic fracture and should be incorporated into the FRAX tool, evaluation of osteoporosis using DXA is expensive and may not be available in some areas. To reduce the investigation costs of this study, we used the FRAX tool without a BMD value for fracture risk assessment. However, the FRAX tool without BMD has been validated in previous studies [41–44]. Those results showed that the 10-year probabilities of major osteoporotic and hip fractures without BMD were significantly correlated to the 10-year probabilities of major osteoporotic and hip fractures with BMD. Additionally, in Thailand, a study of 1038 women showed that FRAX without BMD is a valid tool for predicting osteoporotic fractures at the hip [20]. Due to the high prevalence of asymptomatic vertebral fractures in patients with RA, future study should be focused on the appropriate time and frequency of the screening for vertebral fractures using lateral thoracolumbar spine radiography, as well as the cost-effectiveness of that procedure.

In conclusion, moderate to high 10-year probabilities of major osteoporotic and hip fractures are common among patients with RA. Patients with high cumulative disease activity and functional disability are at high risk for an osteoporotic fracture. Consequently, an osteoporotic fracture risk assessment and a tight control strategy aiming at low disease activity or remission should be routinely performed to reduce future osteoporotic fractures.

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Compliance with ethical standards

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to the principles outlined in the Guideline for Good Clinical Practice International Conference on Harmonization (ICH) Tripartite Guideline (January 1997). The study protocol was approved by local ethics committee, the Siriraj institutional review board.

Disclosures None.

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