

Establishment of a preliminary FRAX®-based intervention threshold for rheumatoid arthritis-associated fragility fracture: a 3-year longitudinal, observational, cohort study

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Abstract

Background: To establish a FRAX®-based prediction model for rheumatoid arthritis (RA)-associated fragility fracture.

Methods: This study is a longitudinal, real-world, registry cohort study. Patients with RA were registered to start in September 2014. The baseline demographics, bone mineral density (BMD), and risk factors of osteoporosis or fragility fracture were recorded. Subsequent fragility fractures during the 3-year observation period were also recorded. We developed a fixed intervention threshold (FITD) to identify fractures by choosing an optimal cut-off point on the receiver operating characteristic (ROC) curve and FRAX®. Several models for intervention thresholds (IT), including fixed intervention threshold (Taiwan) (FITT), age-specific individual intervention threshold (IIT), and hybrid intervention threshold (HIT), were compared to evaluate which IT model will have better discriminative power.

Results: As of December 2020, a total of 493 RA participants have completed the 3-year observation study. The mean age of the participants was 59.3 ± 8.7 , and 116 (23.5%) new fragility fractures were observed during the study period. In terms of pairwise comparisons of area under the curve (n , 95% confidence interval) in the ROC curve, the FITD (0.669, 0.610–0.727, $p < 0.001$) with a value of 22% in major osteoporotic fracture and FITT (0.640, 0.582–0.699, $p < 0.001$) is significantly better than reference, but not for IIT (0.543, 0.485–0.601, $p = 0.165$) and HIT (0.543, 0.485–0.601, $p = 0.165$).

Conclusion: An optimal FIT is established for intervention decisions in RA-associated fragility fractures. This model can offer an easy and simple guide to aid RA caregivers to provide interventions to prevent fragility fractures in patients with RA.

Keywords: fragility fracture, FRAX, interventional threshold, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that manifests as symmetrical, progressive, and erosive arthritis.¹ It has been well documented that patients with RA have a higher risk of osteoporosis and fragility fractures

compared with the general population.^{2,3} Factors including disease activity, aging, steroid use, 25(OH) vitamin D levels, smoking, immobility, and sarcopenia are associated with the risk of bone loss and fractures in patients with RA.^{4,5}

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The Fracture Risk Assessment Tool (FRAX®) has been used universally for the purpose of fracture risk assessment since its release in 2008.⁶ After FRAX® started to be used in clinical practice, the notion of an intervention threshold (IT) to guide intervention decision-making was adopted worldwide.⁷ The IT of each country could be categorized as age-dependent IT, FIT, economic thresholds, or HIT, based on different definitions for high fracture risk.⁷

RA patients not only have a higher 10-year probability of fragility fractures than the general population^{8,9} but also have an imminent fracture risk.¹⁰ Therefore, RA is incorporated as a dichotomous predictor in the WHO FRAX algorithm for predicting the 10-year risk of major osteoporotic fracture (MOF) or hip, which is commonly known as the FRAX score.¹¹ An algorithm for the management of patients at risk of osteoporotic fractures is currently available.¹² Furthermore, guidelines for the management of glucocorticoid-induced osteoporosis also have been released.^{13,14}

Several factors related to RA disease entities, such as disease activity or duration and positivity/titer of autoantibodies, are well-known risk factors of fragility fractures for patients with RA.¹⁵ Consequently, an RA-specific guideline is needed to facilitate interventions for patients with RA with a high risk of fragility fractures. However, at present, no guidelines specifically for the management of RA-associated fractures are available. Our previous investigation demonstrated that anti-osteoporosis therapy can effectively prevent RA-associated bone loss.¹⁶ Therefore, it is crucial now to establish a guideline for the management of RA-associated fractures for RA caregivers.

The primary objective was to determine an optimal cut-off FRAX score for MOF (hip, clinical spine, distal forearm, and proximal humerus fracture), namely a fixed intervention threshold developed (FITD), to build an IT specifically for patients with RA that could best identify future RA-associated fragility fractures, thereby allowing better management. The secondary objective was to compare the accuracy of the model established FITD, via this study, with other recognized models, including fixed intervention threshold in Taiwan (FITT), age-specific individual IT (IIT), and HIT.⁷

Materials and methods

Study population and design

The inclusion criteria for participants and the methods for this study have been shown previously.¹⁵ The reporting of this study conforms to the STROBE statement.¹⁷ This is a 3-year RA osteoporosis/fracture registry study at Kaohsiung Chang Gung Memorial Hospital, which started on 1 September 2014. All RA patients met the 1987 American Rheumatology Association's (ACR) revised criteria or the 2010 ACR/European League against Rheumatism classification criteria.^{18,19} Clinical assessments included demographic data, duration of disease, comorbidities, and history of cigarette smoking and alcohol consumption. We collected information about current medications including glucocorticoid (GC) and biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) at the time of registration. In addition, lifestyle, previous fragility fractures, and other risk factors of fragility fractures on the FRAX® were also recorded. The FRAX scores for MOF, calculated by the FRAX® with femoral neck (FN) BMD (Taiwan version), of each patient were collected. A new incident of fracture was defined as any new symptomatic fragility fracture, including the forearm, hip, pelvis, and humerus fractures or morphometric fractures at vertebrae proved by roentgenography. The BMD at total hip (TH), femoral neck (FN), and lumbar spine (L1-4) was measured using a dual-energy X-ray absorptiometry scanner (Delphi A; Hologic Corp., Waltham, MA, USA). To fulfill the criteria of FRAX score calculations, only participants aged 40–90 years were enrolled.

Written informed consent was obtained from all participants. This study was approved by the local Institutional Review Board of Chang Gung Memorial Hospital (104-3530B, 201901054B0) and was performed according to the principles of the Declaration of Helsinki.

Definition of intervention threshold

Fixed intervention threshold Taiwan (FITT). The Taiwan Osteoporosis Association (TOA) proposed that if an individual's MOF, calculated by the FRAX®, is equal to or over 20%, then the individual will be categorized as having a high risk of fragility fracture and needs intervention and

pharmacologic therapy.²⁰ Therefore, we defined the FITT as equal to or over 20% of MOF in this study.

Individual intervention threshold (IIT). The definition of IIT has been described previously.^{21,22} Based on the notion that one fragility fracture can predict another fracture and that a history of fragility fracture merits intervention, we defined 'IIT' as the FRAX score (10-year probability of fracture) calculated by entering the participant personal variables, including age, gender, weight, and height but assuming that the individual had an only history of the previous fracture and without other clinical risk factors in FRAX tool. Once the IIT of the individual was determined, we recalculated the actual FRAX score of the same participant by inputting the real situation. If the participant's FRAX score for MOF was higher than or equal to the IIT of the same participant, we categorized the participant's fracture risk as above or equal to IIT.

Hybrid intervention threshold (HIT). Hybrid intervention threshold (HIT) is a combination of IIT and FITT. If the participant fulfills the criteria of either IIT or FITT, then the fracture risk of the participant is deemed to have met the criteria of HIT.

Fixed intervention threshold developed (FITD) in the present study. The FITD was determined by searching for the optimal cut-off point in identifying new fragility fractures within the 3-year observation period in our cohort by using the receiver operating characteristic (ROC) threshold that gave the maximum Youden's Index (equal to the sensitivity plus the specificity minus 1).²³

Statistics

Descriptive analysis was presented as the mean with standard deviation or frequency with percentage. The means between two independent groups were examined using the Student's *t*-test, whereas categorical variables were evaluated by the chi-square test or Fisher's exact test. All statistical analysis was considered significant if *p*-values were less than 0.05. We performed all statistical analyses using the Statistical Package for the Social Sciences (SPSS, version 22, Chicago, IL, USA). Power and Sample Size (PASS) calculation software version 14 was used

to make the sample size estimation and power calculations for ROC analyses.

Results

Patient baseline demographic variables

A total of 651 participants were enrolled in the current registry since September 2014, and 532 patients completed the 3-year observation period, which ended in February 2021. A total of 39 participants were excluded for analysis to fulfill the requirement of participants being aged between 40 and 90 in FRAX® at the time of enrollment. The disposition of participants is illustrated in Figure 1. The demographics and clinical characteristics of the enrolled 493 participants and whether they developed new fragility fractures or not are illustrated in Table 1. During the 3-year observation period, 116 (23.5%) participants developed new fragility fractures, including clinical or morphometric fractures, which was confirmed by roentgenography. Compared with the non-fracture group, participants with new fragility fractures were older ($p < 0.001$), had more previous histories of fractures ($p < 0.001$), had higher rates of osteoporosis ($p = 0.005$), had longer disease duration ($p = 0.001$), and had a significantly lower baseline BMD at the three measured sites (all $p < 0.001$). In addition, the FRAX score, major or hip, in the fracture group was significantly higher (27.7 ± 15.7 versus 17.0 ± 8.6 , $p < 0.001$ and 13.7 ± 12.2 versus 6.9 ± 8.6 , $p < 0.001$) than the non-fracture group, respectively.

The optimal cut-off point of FITD, the FRAX score (major), was set at 22.0% by using the ROC threshold for 10-year major osteoporotic fracture risk (Figure 2). As all participants who met the FITT criteria (FRAX score $\geq 20\%$) also fit the criteria of IIT, the participants in the IIT and HIT models were completely the same. Therefore, only the demographics and clinical characteristics of participants who fulfilled the criteria of FITD, FITT, and IIT are presented in Table 2. There were 168 (37.0%), 189 (38.3%), and 431 (87.4%) participants in each category, respectively. Among the groups, there are significant differences in age ($p < 0.001$), gender ($p = 0.008$), disease duration ($p = 0.034$), history of previous fractures ($p < 0.001$), rate of osteoporosis ($p < 0.001$), BMD at all sites (all $p < 0.001$), and FRAX score

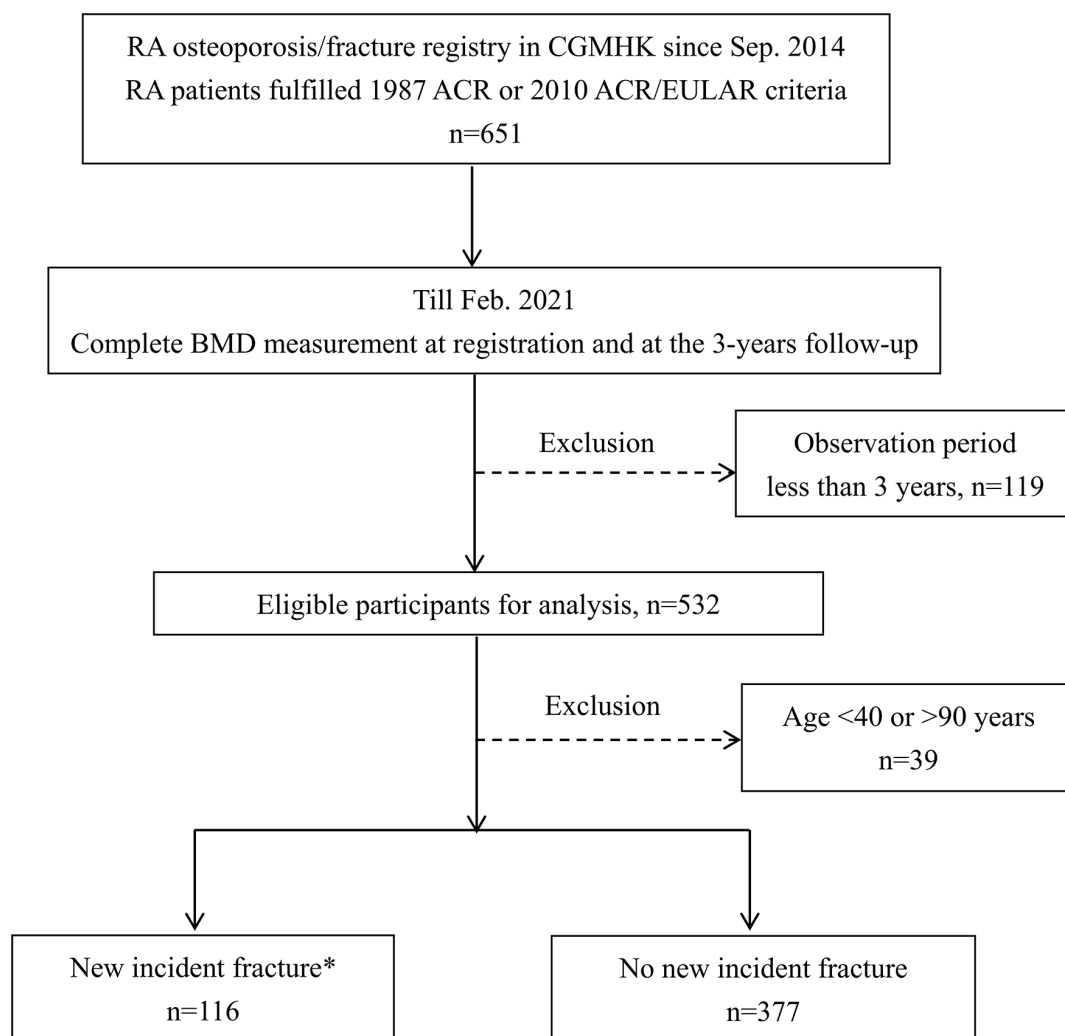


Figure 1. Disposition and grouping of participants.

ACR, American College of Rheumatology; BMD, bone mineral density; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.

*Evidence of new clinical or morphometric fracture.

(major or hip) (all $p < 0.001$). Post hoc analysis of the clinical characteristics between the FITD and IIT groups revealed that the participants in FITD were significantly older ($p < 0.001$), had more previous fractures ($p < 0.001$), had higher rates of osteoporosis ($p < 0.001$), had lower BMD at all sites (all $p < 0.001$), and had higher FRAX scores (major or hip) (all $p < 0.001$).

Comparison among the models to predict new fragility fractures

The subjects included in the IIT and HIT model are completely the same. A comparison of the three models (FITD, FITT, and IIT) in the

prediction of fragility fractures is illustrated in Table 3. The FITD, FITT, and IIT models identified 69, 69, and 108 participants with new major fragility fractures during the study period, respectively. The area under the curve (AUC) (n , 95% CI) of FITD and FITT was 0.669 (0.610–0.727) and 0.640 (0.582–0.699), respectively, and was significantly different ($p < 0.001$, $p < 0.001$) from that of the reference but not that of IIT [0.543 (0.485–0.601)]. In terms of AUC (n , 95% CI) comparisons between the models, FITD and FITT were significantly higher than IIT ($p < 0.001$, $p < 0.001$), but FITD and FITT were quite similar ($p = 0.482$). In the comparisons between FITD and FITT, all of the parameters in

Table 1. Characteristic of total participants and participants with and without new fragility fractures.

Variables	Total N=493	New fracture N=116	Non-new fracture N=377	<i>p</i> ^a
Age (years)	59.3 ± 8.7	62.6 ± 8.3	58.3 ± 8.6	<0.001
Female, <i>n</i> (%)	421 (85.4)	104 (89.8)	317 (84.1)	0.137
Body mass index (kg/cm ²)	23.8 ± 4.0	23.9 ± 3.7	23.8 ± 4.1	0.775
RA-related factors				
Disease duration (years)	13.8 ± 9.1	16.4 ± 9.4	13.1 ± 8.9	0.001
RF+, ^b <i>n</i> (%)	327 (66.3)	84 (73)	243 (64.6)	0.094
ACPA+, <i>n</i> (%)	332 (67.3)	79 (68.7)	253 (69)	0.890
Baseline DAS28-ESR	3.3 ± 1.2	3.6 ± 1.2	3.2 ± 1.2	0.009
Mean DAS28-ESR	3.1 ± 0.9	3.3 ± 1.0	3.0 ± 0.9	0.018
HAQ-DI	0.61 ± 0.74	0.87 ± 0.90	0.53 ± 0.67	0.001
ESR, mm/h	23.6 ± 20.7	25.0 ± 21.1	23.1 ± 20.5	0.394
CRP, mg/L	2.3 (6.5)	2.3 (6.2)	2.8 (8.6)	0.372
Fracture risk factors+ ^c				
Previous fracture, <i>n</i> (%)	163 (33.1)	66 (56.9)	97 (25.7)	<0.001
Secondary osteoporosis, <i>n</i> (%)	21 (4.3)	5 (4.3)	16 (4.2)	0.975
GC exposure, <i>n</i> (%)	456 (92.5)	111 (95.7)	345 (91.5)	0.135
Parent fractured hip, <i>n</i> (%)	39 (7.9)	9 (7.8)	30 (7.9)	0.299
Smoking, <i>n</i> (%)	31 (6.3)	6 (5.2)	25 (6.6)	0.667
Alcohol, <i>n</i> (%)	6 (1.2)	2 (1.7)	4 (1.1)	0.569
Osteoporosis, <i>n</i> (%)	144 (29.2)	46 (40.4)	98 (26.5)	0.005
BMD (g/cm ²)				
FN	0.626 ± 0.116	0.586 ± 0.101	0.638 ± 0.117	<0.001
TH	0.785 ± 0.139	0.734 ± 0.136	0.800 ± 0.137	<0.001
L1-4	0.860 ± 0.167	0.811 ± 0.165	0.874 ± 0.165	<0.001
FRAX score (%)				
Major	19.3 ± 13.8	27.7 ± 15.7	17.0 ± 8.6	<0.001
Hip	8.5 ± 10.0	13.7 ± 12.2	6.9 ± 8.6	<0.001
<p>ACPA, anti-citrullinated protein antibodies; BMD, bone mineral density; DAS28-ESR, disease activity score-28 joint-erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FN, femoral neck; FRAX, Fracture Risk Assessment; GC, glucocorticoid; HAQ-DI, health assessment questionnaire disability index; L1-4, 1st-4th lumbar vertebra; RA, rheumatoid arthritis; RF, rheumatoid factor; TH, total hip.</p> <p>Values are presented as mean ± standard deviation or median (interquartile range) unless otherwise mentioned.</p> <p>^aComparison between new fracture and non-new fracture groups.</p> <p>^bPresence.</p> <p>^cDefined as in FRAX tool.</p>				

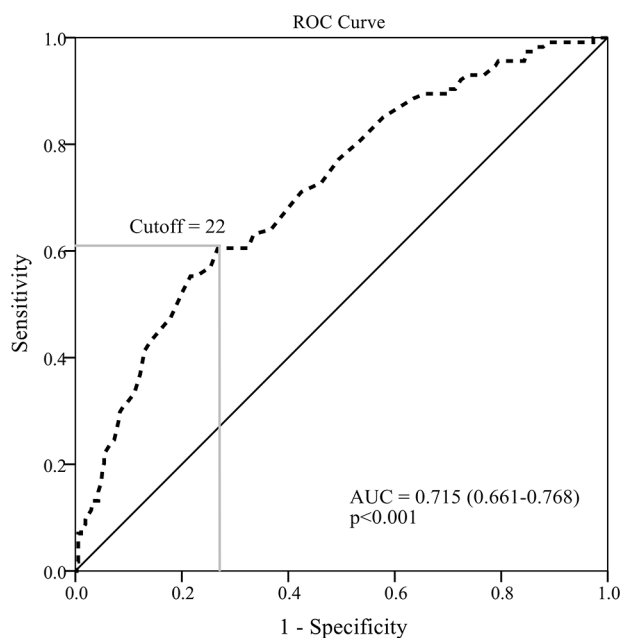


Figure 2. Receiver-operating characteristic [ROC] curve for the 10-year risk of major osteoporotic fracture of the current study.

predicting fragility fractures were better for FITD than FITT. The sensitivity (%; 95% CI) of IIT was (95.6, 89.5–98.4) and was higher than that of FITD (61.1, 51.4–70) and FITT (61.1, 51.4–70) but had lower specificity (%; 95% CI) (12.9, 9.8–16.9) than that of FITD (73.3, 68.5–77.7) and FITT (67.7, 62.6–72.3). FITD had the highest positive predictive value (%; 95% CI) (41.1, 33.6–48.9), while IIT had the highest negative predictive value (%; 95% CI) (90.6, 78.6–96.5) among the models. In terms of the positive likelihood ratio, FITD had the highest one (%; 95% CI) (2.3, 1.8–2.9) among the models. The power of this study was 95% when detecting a difference of 0.126 between FITD with an AUC of 0.543 and IIT with an AUC of 0.669 using a one-sided z -test at a significance level of 0.05.

Discussion

In this study, we compared the performance of commonly used intervention tools for fragility fractures namely FIT, IIT, and HIT. We aimed to provide a better modality to help RA caregivers in identifying patients with RA with a high risk of fragility fractures and thus offer efficient and early intervention. Via this investigation, we found that FITD is a better model than FITT and IIT in identifying patients with RA who developed

fractures during the 3-year observation period on a real-world basis.

Since the advent of FRAX® in 2008, three major approaches have been utilized to develop IT with FRAX®, namely FIT, age-dependent IT, and HIT. The FIT was set from 4% to 20% for a major fracture and 1.3–5% for a hip fracture in some countries and organizations.⁷ However, no rationale was provided by any of these countries, including Taiwan, or organizations for the FIT apart from the NOF (National Osteoporosis Foundation) of the United States.⁷ The Taiwan Osteoporosis Practice guideline adopts US thresholds (10-year probability of MOF higher than 20% and hip fracture higher than 3%), drawing on expert advice, but no national analysis and data were available.²⁰ A comparative study at a mean 4.5-year follow-up showed the clinical utility of NOF, NOGG (National Osteoporosis Guideline Group, UK), and Taiwanese guidelines to treatment strategies for fracture prevention among Chinese postmenopausal women is low as reflected by the poor clinical utility index.²⁴ Therefore, efforts to develop a specific set of interventions for RA patients to guide osteoporosis treatment are warranted.

The age-dependent IT was first proposed by the NOGG²⁵ and suggested by Kanis *et al.*¹² in a

Table 2. Characteristics of RA participants fulfilled the criteria of FITD, FITT, and IIT.

Variables	FITD N=168	FITT N=189	IIT N=431	p ^a
Age (years)	65.2 ± 7.1	64.9 ± 7.2	59.6 ± 8.8	<0.001
Female, n (%)	156 (92.9)	173 (93.1)	371 (86.1)	0.008
BMI (kg/cm ²)	23.6 ± 3.7	23.5 ± 3.7	23.9 ± 4.0	0.679
RA-related factors				
Disease duration (years)	15.2 ± 8.9	15.5 ± 9.1	13.8 ± 9.0	0.034
RF+, ^b n (%)	118 (70.2)	130 (68.8)	287 (66.5)	0.574
ACPA+, n (%)	121 (72)	138 (70)	293 (68)	0.328
Baseline DAS28-ESR	3.5 ± 1.2	3.5 ± 1.2	3.3 ± 1.2	0.061
Mean DAS28-ESR	3.2 ± 0.9	3.2 ± 1.0	3.1 ± 0.9	0.275
HAQ-DI	0.90 ± 0.87	0.88 ± 0.86	0.62 ± 0.75	<0.001
ESR, mm/h	27.2 ± 21.5	27 ± 21.2	23.9 ± 21	<0.001
CRP, mg/L	3.3 (8.2)	3.1 (8.3)	2.5 (6.6)	0.191
Fracture risk factors+ ^c				
Previous fracture, n (%)	116 (69)	122 (64.6)	158 (36.7)	<0.001
2nd osteoporosis, n (%)	6 (3.6)	10 (5.3)	19 (4.4)	0.733
GC exposure, n (%)	167 (99.4)	186 (98.4)	418 (97)	0.154
Parent fractured hip, n (%)	20 (11.9)	22 (11.6)	39 (9)	0.784
Smoking, n (%)	3 (1.8)	3 (1.6)	26 (6)	0.009
Alcohol, n (%)	2 (1.2)	2 (1.1)	6 (1.4)	0.938
Osteoporosis, n (%)	95 (56.5)	103 (54.5)	133 (30.9)	<0.001
BMD (g/cm ²)				
FN	0.543 ± 0.082	0.547 ± 0.796	0.630 ± 0.114	<0.001
TH	0.694 ± 0.117	0.699 ± 0.117	0.780 ± 0.140	<0.001
L1-4	0.767 ± 0.142	0.771 ± 0.138	0.851 ± 0.167	<0.001
FRAX score (%)				
Major	35.2 ± 11.1	33.6 ± 11.5	21.1 ± 13.5	<0.001
Hip	18.3 ± 11.3	17.1 ± 11.2	9.4 ± 10.3	<0.001

ACPA, anti-citrullinated protein antibodies; BMD, bone mineral density; BMI, body mass index; DAS28-ESR, disease activity score-28 joint-erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FITD, Fixed intervention threshold developed in the present study; FITT, Fixed intervention threshold Taiwan; FN, femoral neck; FRAX, Fracture Risk Assessment; GC, glucocorticoid; HAQ-DI, health assessment questionnaire disability index; IIT, individual intervention threshold; L1-4, 1st-4th lumbar vertebra; RA, rheumatoid arthritis; RF, rheumatoid factor; TH, total hip. Values are presented as mean ± standard deviation or median (interquartile range) unless otherwise mentioned.

^aComparison among three groups.

^bPresence.

^cDefined as in FRAX tool.

Table 3. Comparison of parameters in prediction of fragility fracture among models.

Models	Fractures (n) ^a	AUC ^b	Sensitivity ^b	Specificity ^b	PPV ^b	NPV ^b	LR+	LR-
FITD	69	66.9 (61.0–72.7)	61.1 (51.4–70.0)	73.3 (68.5–77.7)	41.1 (33.6–48.9)	86.1 (81.7–89.6)	2.3 (1.8–2.9)	0.5 (0.4–0.7)
FITT	69	64.0 (58.2–69.9)	61.1 (51.4–70.0)	67.7 (62.6–72.3)	36.5 (29.7–43.8)	85.1 (80.4–88.8)	1.9 (1.5–2.3)	0.6 (0.5–0.7)
IIT	108	54.3 (48.5–60.1)	95.6 (89.5–98.4)	12.9 (9.8–16.9)	25.1 (21.1–29.5)	90.6 (78.6–96.5)	1.1 (1.0–1.2)	0.3 (0.1–0.8)

AUC, area under the curve; FITD, fixed intervention threshold developed in the present study; FITT, fixed intervention threshold Taiwan; IIT, individual intervention threshold; LR, likelihood ratio; LR+, probability of an individual with the condition having a positive test/probability of an individual without the condition having a positive test; LR-, probability of an individual with the condition having a negative test/probability of an individual without the condition having a negative test; NPV, negative predictive value (probability that the disease is not present when the test is negative); PPV, positive predictive value (probability that the disease is present when the test is positive).

^aNumber of predicted fractures.

^bData presented as % (95%, confidence interval).

recent article. However, those who calculate age-dependent IT assumed all of the individuals' body mass index (BMI) to be 24 kg/m². Clearly, this is not reasonable as the FRAX score can be remarkably different in individuals with different BMIs. In addition, the mean BMI of women in Taiwan is 22.5 kg/cm².²⁶ Therefore, when using the FRAX® (Taiwan version), it was decided that we would use the IIT in this investigation and our previous publication²⁰ rather than the prototype age-dependent IT.

It is widely acknowledged that the application of FRAX® should be country-specific. However, as FRAX® has progressively become more widely utilized globally, it was realized that the use of FRAX® not only should be ethics-specific²⁷ but also should be disease-specific^{28–30} when applied in precision medicine. As previously mentioned, RA has been incorporated as a dichotomous predictor in the FRAX®; however, no RA-specific guidelines or recommendations, as of GIOP,^{13,14} based on FRAX® are available currently. Several factors, including disease duration, menopause duration, cumulative disease activity, cumulative functional disability,³¹ presence of anti-citrullinated protein/peptide antibodies,¹⁵ and medications,³² have been proposed to be associated with the FRAX score. It suggests that the FRAX® could not precisely assess the risk of RA-related fragility fractures as it does not take into account the factors that are well known for being independent fracture risk factors in RA. In addition, Corinne Klop *et al.*³³ demonstrated that the FRAX® overestimated

fracture risks in patients with RA in the United Kingdom. Therefore, it is necessary to develop a new and simple guideline or IT, based on real-world data and FRAX®, to help RA caregivers decide which RA patients need intervention for fragility fractures.

In this investigation, we made use of the data collected in a long-term, registry, real-world, observational study for RA-related osteoporosis/fractures to establish a preliminary IT to potentially expedite intervention. As all of the parameters in the prediction of fragility fractures of FITD were better than those of FITT, we will focus on the discrimination power between FITD and IIT in the subsequent discussion. We found that FITD was superior to IIT ($p < 0.001$) in terms of AUC. This indicated that FITD had a better discrimination power in identifying RA patients with a fragility fracture than IIT. Despite the very high sensitivity in the IIT [95.6 (89.5–98.4)] model, its AUC is only approximately 50%. In addition, the positive LR for FITD was 2.3 (1.8–2.9) and higher than the positive LR of IIT [1.1 (1.0–1.2)], which suggests FITD was at least 15% higher in predicting fractures than IIT.³⁴

Our study has several important strengths. The FITD was derived from a longitudinal, real-world, observation, cohort study. In addition, incidents of fractures, including confirmed asymptomatic morphometric fractures by radiographs, captured during the observation period represented the summary effect of the aforementioned RA-related factors and risk factors in

FRAX®. Although the FIT has been adopted in several countries, they lack a statistical basis, unlike the FITD in the current investigation. This approach had never been attempted before for FIT in intervention or therapeutic decisions. In addition, only a previous investigation³⁵ focused on the discrimination in decisions for osteoporosis treatment based on the FRAX® and BMD in patients with RA. To the best of our knowledge, no study has investigated the discrimination power, including AUC, sensitivity/specificity, and so on, among the models of IT. Using the approach in this study, we determined that FITD set at (22%) is a better model than IIT and is an optimal cut-off point for our RA cohort. Our study demonstrated the distinctiveness of a different approach and the predictive performance and provided real-world evidence for a potential candidate-identification system for intervention in patients with RA. Finally, in terms of applications, compared with IIT, FITD is much easier to use in making intervention decisions for patients with RA. The caregiver only needs one step: use the FRAX® and memorize the number (22%) of the FITD to decide whether to conduct interventions.

The study has several limitations. First, the FRAX® was designed for the estimation of the 10-year fracture probability. The observation period was 3 years in this study. Whether the model developed in this investigation for the prediction of fractures in 3 years can also have a better discrimination power than other models in 10 years is not certain. A large clinical registry for the province of Manitoba, Canada, showed that FRAX can predict incident major bone and hip fractures in women and men aged 40 years and older over intervals shorter and longer than 10 years, spanning 1–15 years.³⁶ On the basis of that study and our results, we believe that this assessment tool for patients with RA, even if intended for 10-year fracture risk, has been useful in a shorter observation. Apart from this, the FRAX score, either major or hip, in the new fracture group is significantly higher than that of the non-new fracture group (Table 1). This suggests that the FRAX score can predict fragility fractures efficiently in the 3-year observation in our cohort. Second, our findings are specific to the Taiwanese context; it is unclear whether this model can be applied in other countries or ethics with a similar approach. Third, only the FRAX score (major) was adopted in developing the

FITD in this study, and whether the FRAX score (hip) can also have the same discrimination power is not known. Finally, the establishment of FRAX® was based on several meta-analysis studies that incorporated data from more than 200,000 participants. The approach developed in this study has a relatively small sample size, with a relatively low AUC level. However, confirmation of our observations for patients with RA will require future investigation in a larger cohort with longer duration of follow-up.

Conclusion

This study illustrated that FITD is an adequate model in case-finding in patients with RA for intervention for fragility fractures. Future validation studies on this prediction model for fragility fractures in RA are necessary.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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