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Appropriate FRAX® Intervention Threshold for Pharmacological Treatment of Osteoporosis in Thailand

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Purpose: The Fracture Risk Assessment Tool (FRAX®) has been recommended and incorporated into osteoporotic guidelines worldwide to assess fracture risk and promptly diagnose osteoporosis when bone mineral density is unavailable. However, a country-specific intervention threshold for Thai patients remains unknown. Therefore, we aimed to identify an appropriate cut-off point for the 10-year probability of hip fracture (HF), specifically in the Thai population.
Methods: This retrospective cohort study included members of the Thai population aged 50-90 years, enrolled from January 2018 to January 2020. Analysis of data collected from online FRAX® tool questionnaires was conducted and the receiver operating characteristic (ROC) curve was used to determine a new appropriate cut-off value as the intervention threshold.
Results: A total of 1,311 (HF: 422 [32.2%], non-HF: 889 [67.8%]) participants were included. The FRAX® 10-year probability of fracture in patients with HF was significantly higher than in non-HF (5.8% ± 4% vs. 4.7% ± 4.5%, respectively; $P < 0.01$), whereas the probability of major osteoporotic fracture (MOF) was similar (11.0 ± 5.8% vs. 10.6 ± 6.2%, $P = 0.27$). The ROC curve revealed a new intervention threshold for the FRAX®-based 10-year risk for HF of 4.3% with a maximum area under the curve (AUC) (95% confidence interval: 0.632 (range: 0.602-0.663; $P < 0.001$), with sensitivity and specificity of 62.9% and 60.7%, respectively.
Conclusions: The intervention threshold cut-off value for osteoporosis treatment among the Thai population was 4.3%, which is higher than the cut-off point recommended in the Thai national guidelines.

Keywords: FRAX® intervention threshold, osteoporosis, Thailand, major osteoporotic fracture, hip fracture

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Osteoporosis is one of the most common health concerns among older adults. The consequences of reduced bone mineral density (BMD) may be severe. Hip fractures (HF) and other major osteoporotic fractures (MOFs) significantly affect morbidity and mortality. These conditions also impose a high economic burden on health care services. There has been an exponential growth in the geriatric population in Thailand; therefore, early osteoporosis diagnosis and timely administration of anti-osteoporotic medication to prevent fractures is vital[1].

Dual-energy X-ray absorptiometry (DXA) is the quantitative gold standard for diagnosing osteoporosis. However, this assessment cannot be adopted as a standard screening tool in clinical practice in Thailand because it is not easily accessible and is relatively expensive. Because of limited testing, many patients remain undiagnosed, causing therapeutic delays and potentially fatal complications[2]. Hence, a cost-effective screening tool with an appropriate intervention threshold for osteoporosis treatment should be identified.

In 2011, the Fracture Risk Assessment Tool (FRAX®) was developed by the University of Sheffield, and since then, it has been used globally to estimate the likelihood of MOF and HF in the next ten years. This tool is also used to screen for and initiate anti-osteoporotic medication based on the intervention threshold. The inclusion of the FRAX® tool in over 100 national guidelines, including Thailand, in conjunction with the incorporation of osteoporosis fracture prevention in national policy, has resulted in rapid and significant impact on its use[3]. In Thailand, an increase in access to the FRAX® website has been observed.

Although the FRAX® tool is country-specific and has been utilized in many osteoporotic guidelines worldwide[4-7], the references for intervention thresholds used in Thailand are based on the National Osteoporosis Foundation (NOF) of the United States[5,8]. However, this reference may not be appropriate for the Thai population. Currently, the ideal intervention threshold for Thai patients remains unclear. Therefore, this research aimed to identify an appropriate 10-year probability cut-off point for HF intervention among the Thai population.

METHODS

Study design

In this retrospective cohort study, we analyzed data collected from questionnaires for online FRAX® tool evaluation of 1,311 patients aged 50–90 years who were seen at the osteoporosis and metabolic bone clinic, Department of Orthopedics, who were admitted for review and omitted for review, from January 2018 to January 2020. The exclusion criteria were high-energy trauma and pathological fracture. The subjects were then assigned to two groups: HF and non-HF. The collected information was processed using FRAX® tools. The 10-year probabilities of HF and MOF were calculated and analyzed to identify the intervention threshold cut-off point for the Thai population.

Fracture risk assessment tool (FRAX®)

The FRAX® tool was used to assess fractures in both males and females by using 12 factors through logistic regression. This tool was accessed via the following website: https://www.sheffield.ac.uk/FRAX/. The details of each clinical factor, including sex, weight, height, previous fracture, underlying diseases, parental history of HF, smoking, and alcohol use, were obtained from the hospital database at the time of the patient's initial visit as a part of the fracture liaison service, and were considered as risk factors for osteoporotic fractures. The results were recorded as a percentage of the 10-year probability of developing HF and MOF. By combining this information with the subject femoral neck bone mineral density (FN BMD), the accuracy of the predicted percentage would increase. As the probability of fracture differed between countries, the Thai FRAX® tool was available from the aforementioned website. All patients with previous osteoporotic fracture were recorded as having a history of previous osteoporotic fracture, while patients with recent HF were recorded as having no previous osteoporotic fracture to avoid a selection bias for data interpretation of the 10-year probability of having HF and MOF.

Statistical analysis

All patient demographic data in HF and non-HF, including age, sex, weight, height, body mass index (BMI; kg/m^2), smoking status, alcohol consumption, steroid intake, history of previous osteoporotic fracture, secondary osteoporosis, history of parental hip fracture, underlying diseases of rheumatoid arthritis, femoral neck BMD (g/cm^2), and T-score, were tested using independent *t*-test and Fisher's exact test to identify correlations between the two groups. Statistical significance was set at p <0.01. The results of the FRAX® tool were examined using a receiver operating characteristic (ROC) curve to determine the cut-off point of the new intervention threshold for both HF and MOF with maximal area under the curve (AUC), along with a maximal Youden index (J = max (sensitivity+ specificity -1))[9]. All data were calculated using SPSS version 25 (IBM Corp., Armonk, NJ, USA)

RESULTS

Patient demographic data

A total of 1,311 subjects were included in this study; 422 subjects (32.2%) with HF at the time of admission and 889 (67.8%) without HF. The patient characteristics are summarized in Table 1. The HF group was significantly older (78 ± 9 vs. 70 ± 10 years; P < 0.01) with lower BMI (22.1 ± 3.8 vs. 23.5 ± 3.9; P < 0.01) and FN BMD before treatment (0.6 ± 0.1 vs. 0.7 ± 0.1 g/cm^2, P < 0.01) compared to the non-HF group. The non-HF group comprised significantly more female patients (91.6% vs. 76.3%; P < 0.01), with higher glucocorticoid usage (15% vs. 2.8%; P < 0.01), secondary osteoporosis (5.8% vs. 2.4%; P < 0.01), and parental HF (5.7% vs. 4.5%, P < 0.01).

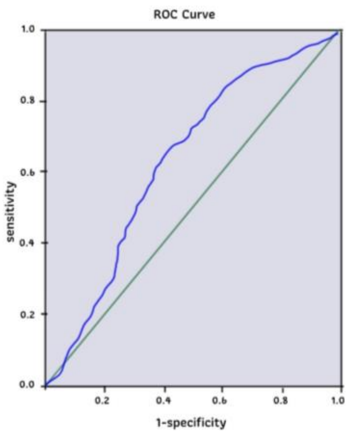
The average FRAX® 10-year probability of fracture in patients with HF was significantly higher than that in non-HF patients (5.8% ± 4% vs. 4.7% ± 4.5%, respectively; P < 0.01) (Table 1). In contrast, there was no significant between-group difference in FRAX® 10-year probability of having MOFs (11.0 ± 5.8 vs. 10.6 ± 6.2; P = 0.27).

ROC curve and appropriate FRAX® intervention threshold for the Thai population

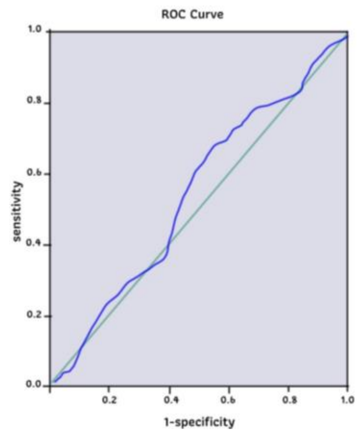
The ROC curve revealed a new intervention threshold for FRAX®-based 10-year risk for HF of 4.3%, with a maximum AUC (95% confidence interval [CI]: 0.632 [range: 0.602–0.663]; P < 0.001. The sensitivity and specificity were 62.9 and 60.7%, respectively (Fig. 1A). The recommended intervention threshold for FRAX® 10-year likelihood of MOF was 10%, with AUC (95%CI: 0.541 (range: 0.508–0.574); P = 0.016 (Fig. 1B).

Table 1 Comparison of clinical parameters and average FRAX® 10-year fracture risk among patients with hip fracture and non-hip fracture.

Variables	Hip fracture (N = 422)	Non-hip fracture (N = 889)	p-value
Female Sex, n (%)	322 (76.3)	815 (91.6)	<0.01
Age (years)	78 ± 9	70 ± 10	<0.01
Weight (kg)	55 ± 11	54 ± 10	0.19
Height (m)	1.6 ± 0.1	1.5 ± 0.1	<0.01
Body mass index (kg/m^2)	22.1 ± 3.8	23.5 ± 3.9	<0.01
Femoral neck BMD (g/cm^2)	0.6 ± 0.1	0.7 ± 0.1	<0.01
Femoral neck T-score	-2.4 ± 1	-1.8 ± 0.9	<0.01
Cigarette smoking, n (%)	8 (1.9)	12 (1.3)	0.47
Alcohol consumption, n (%)	2 (0.5)	17 (1.9)	0.05
Glucocorticoids usage, n (%)	12 (2.8)	125 (14)	<0.01
Previous osteoporotic fracture, n (%)	177 (41.9)	386 (43.4)	0.63
Secondary osteoporosis, n (%)	10 (2.4)	52 (5.8)	<0.01
Parental hip fracture, n (%)	8 (1.9)	54 (6.1)	<0.01
Rheumatoid arthritis, n (%)	19 (4.5)	51 (5.7)	0.43
FRAX® 10-year risk of MOF (%)	11 ± 5.8	10.6 ± 6.2	0.27
FRAX® 10-year risk of hip fracture (%)	5.8 ± 4	4.7 ± 4.5	<0.01



A) Hip fracture.
Cut-off point: 4.3%
Sensitivity: 62.9%
Specificity: 60.7 %
Area under the curve: 0.63



B) Major osteoporotic fracture.
Cut-off point: 10%
Sensitivity: 55%
Specificity: 54.5%
Area under the curve: 0.54

Fig. 1 Receiver operative characteristic (ROC) curve analysis to determine the appropriate FRAX® intervention threshold for Thais associated with fragility fracture for A) Hip fracture (HF) and B) Major osteoporotic fracture (MOF).

DISCUSSION

The FRAX® tool has been utilized globally to assess the risk of fragility fractures, and it has been incorporated into many national guidelines for treating osteoporosis[5]. However, there is currently no specific population-based intervention threshold for the Thai population. The fixed intervention thresholds derived from this study were 4.3% for the 10-year probability of HF and 10% for the 10-year probability of MOF.

The National Osteoporosis Foundation (N-OF) uses a FRAX®-based intervention threshold of 3% for HF and 20% for MOF, which was derived from a cost analysis[5]. Individuals with a higher 10-year probability of fracture are defined as having a high risk of fracture and are eligible for pharmacological treatment[10]. However, Thai national guidelines only recommend the FRAX®-based intervention threshold of 3% for HF, directly referencing the United States, and did not mention the threshold for MOF[8].

The new HF cut-off value in our study was higher than the previously referenced NOF value. This might be due to the selection of high-risk populations collected from osteoporosis and metabolic bone disease clinics, leading to a high population discrepancy between HF and non-HF populations. Many clinical risk factors for osteoporosis in the patient demographic data corresponded with those in the HF group[11,12]. However, there were some statistically significant differences between non-HF and HF groups, including female sex, history of steroid use, secondary osteoporosis, and positive parental HF status. Notably, this observation could be due to selection bias, as the vast majority of the non-HF data were collected from the older population who attended osteoporosis and metabolic bone disease clinics.

A systematic review of the FRAX®-based intervention threshold demonstrated a disparity in the cut-off point for HF of 1.3–5%, which could be explained by ethnic differences and provides the rationale for establishing such a threshold[5]. However, the results of our study were similar to those of a recent study by Sribenjalak et al.[13], which also found a cut-off point for HF of 4.9% (without BMD) and 4% (with BMD). The aforementioned study was conducted in the northeastern region of Thailand, from which the FRAX® calculator was developed. As a result, the results of this study could be considered for internal validation. However, the participants in our study were from the central region of Thailand and were recruited from two different institutions. The proportion of patients with HF in our study was considerably higher than that in the previous study (32.2% (422/1,311 subjects) vs. 1.6% (45/2,872 subjects). As a result, our study complements and validates the results of the previous study revealing that the cut-off value for the Thai population from FRAX® is not as low as 3% for HF, as indicated in the latest version of the national osteoporosis management guidelines.

The previous MOF fixed intervention threshold from the NOF compared to the MOF intervention threshold in our study was substantially lower (20% vs. 10%, respectively). This result was consistent with the MOF fixed intervention thresholds of other countries, such as 10% for Hong Kong(14), 10% for Japan(15), and 9% for Sri Lanka(16). Recently, Sribenjalak et al. in Thai postmenopausal women proposed a FRAX® intervention threshold of 4.9% for HF and 9.8% for MOF(13). Both values were confirmed by our findings. However, because the participants in the aforementioned study were largely from the hospital database instead of a fracture liaison service, the number of hip fractures in their study was limited, comprising only 1.6% of the sample size. Furthermore, the study did not incorporate other MOFs, including vertebral and wrist fractures, into the calculation, possibly leading to underestimation of patients eligible for anti-osteoporosis medication and questionable ability to detect MOF.

The lower intervention threshold would allow the high-risk population to benefit from receiving early treatment. Nevertheless, with increasing osteoporotic treatment, more patients could be at risk of adverse effects from the medication and complications from procedural treatment. Cheung et al.(14) demonstrated a similar finding when analyzing different strategies to determine an effective intervention threshold for MOF in the Hong Kong population; the fixed cut-off point of 9.95% had the highest sensitivity (62.3%) when compared with the age-dependent threshold or when treating a patient with a history of previous fractures.

Most European countries(17) prefer age-dependent intervention thresholds to minimize overtreatment in the general population with high clinical risk factors. In contrast, many Asian countries, such as Hong Kong (14), Japan(15), Sri Lanka(16), Taiwan(17), China(18), and Malaysia(19), favor the fixed intervention threshold. The fixed intervention threshold has mainly targeted older adults focusing on an absolute high-risk and early postmenopausal population. Lekamwasam et al. revealed the effectiveness of using a revised two-tier fixed intervention threshold for women aged < 70 years and those aged ≥ 70 years as the strategy with the highest specificity for the Sri Lankan population when compared with former fixed, age-dependent, and hybrid intervention thresholds(16). While the fixed intervention threshold appeared to be appropriate in the Thai population where there was no age mapping data available for the general population, referencing a fixed population threshold directly from the NOF without the evidence-based rationale for application to the Thai population has raised concerns, as the health-economic approach based on the American population might not be compatible with the Thai population. Moreover, the study was published over 10 years ago, and healthcare costs have continuously changed(17).

To our knowledge, this is the first study in Thailand to define an appropriate cut-off value for the FRAX intervention threshold using entirely osteoporotic patients with HF and non-HF as the study population. The large sample size collected from two leading hospitals in the central region of Thailand in this research demonstrated similar cut-off points compared to a recent study in the northeastern region, suggesting that central and northeastern Thais could accurately reflect the majority of the older Thai population. The approach used in this study was based on actual patient clinical data. All data were recorded during the initial patient visit. Therefore, recall bias was minimized. Nevertheless, this study has limitations, including the aforementioned selection bias, which could possibly lead to more patients with a history of fragility fracture and secondary osteoporosis, such as glucocorticoid-induced osteoporosis. Furthermore, the health-economic analysis, the key consideration when establishing national guidelines, was not conducted.

Future improvements should be implemented by collecting a community sample with a follow-up period as a prospective cohort to increase the validity of the research. A comparison of one fixed intervention threshold with a two-tier fixed intervention threshold may be beneficial. Finally, a fixed intervention threshold can be further correlated with cost-effectiveness to provide the economic threshold for Thailand.

CONCLUSIONS

The suggested cut-off value for the HF intervention threshold for osteoporosis treatment among the Thai population was 4.3%, which is higher than the recommended intervention threshold in the latest national osteoporosis guidelines, but similar to that of a previous study in the Thai population. This result could play an important role in therapeutic decision making in Thailand.

ETHICAL CONSIDERATIONS

All researchers were certified by the NIDA clinical trial network of good clinical practice and approved by the appropriate ethics review committee for human research (COA no.40/2018).

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