Endocrine (2019) 65:200–206
https://doi.org/10.1007/s12020-019-01951-8

ORIGINAL ARTICLE

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Comparison of strategies for setting intervention thresholds for Chinese postmenopausal women using the FRAX model

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Received: 30 January 2019 / Accepted: 5 May 2019 / Published online: 20 May 2019

Abstract

Purpose The two main strategies for managing osteoporosis using the Fracture Risk Assessment (FRAX®) are the fixed-probability threshold of the National Osteoporosis Foundation (NOF) and the age-dependent-probability threshold of the National Osteoporosis Guideline Group (NOGG), but there are no FRAX® Chinese-specific thresholds. This study examined the NOF and NOGG strategies for intervention thresholds using the Chinese FRAX® model for their appropriateness for Chinese postmenopausal women, and explored Chinese-specific thresholds.

Methods Postmenopausal women ($N = 264$) >50 years old from community-medical centers in China were randomly selected. They completed a self-report questionnaire and underwent bone mineral density measurements and spinal X-rays. The 10-year risks for a major osteoporosis fracture and hip fracture were calculated using the Chinese FRAX® model. Using an osteoporosis diagnosis as the gold standard, we compared the abilities of the NOF and NOGG thresholds to detect osteoporosis by analyzing their sensitivity, specificity, accuracy, and positive and negative likelihood ratios.

Results The 10-year risks for hip fracture and a major osteoporotic fracture increased with age. The NOF's accuracy in detecting osteoporosis was 83.33% and the NOGG's was 74.24%. The NOF thresholds showed higher accuracy and specificity than the NOGG thresholds.

Conclusion NOF thresholds are more appropriate for Chinese menopausal women.

Keywords Osteoporosis · FRAX · Postmenopausal women · Osteoporotic fracture · China

Introduction

Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass and destruction of bone micro-structures, which ultimately leads to increased bone fragility and fracture risk [1]. Osteoporotic fracture is a major cause of disability and death among elderly patients, including the

Supplementary information The online version of this article (https://doi.org/10.1007/s12020-019-01951-8) contains supplementary material, which is available to authorized users.

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devastating consequences of hip fracture, which is usually followed by large personal and socio-economic burdens. The mortality rate of hip fracture within 1 year has been reported to be 27%, which is 8 times higher than that of the general population older than 60 years of age [2]. According to 2015 forecast, medical expenses for osteoporosis-related fractures in China in 2035 and 2050 will reach $18.9 and $25.43 billion, respectively [3].

Given the increase in the osteoporosis population, people have gradually attached greater importance to osteoporosis, but lack awareness of the hazards of osteoporosis. Most individuals who have had osteoporosis-related fractures or are at high risk for fractures are not being diagnosed, and those who are diagnosed are not following up with regular treatment; therefore, the number of patients receiving treatment for osteoporosis is decreasing [4, 5]. Osteoporosis requires early prevention, detection, and treatment, before the occurrence of a fragility fracture. A related concern is the availability of effective osteoporotic treatments to reduce the risk of further fractures after the first occurrence of a fragility fracture [5]. Hence, routine prevention, early diagnosis, and treatment are essential for osteoporosis management.

The Fracture Risk Assessment (FRAX®) algorithm was developed to assess the risk for hip fracture or a major osteoporotic fracture among men and women based on clinical risk factors, combined with or without inclusion of femoral neck bone mineral density (BMD), which is available online (www.shef.ac.uk/FRAX) [6]. BMD measurements and treatment are recommended for patients with a high risk of fracture who have been screened using FRAX® thresholds. Based on guidelines from different countries, there are two main types of reference thresholds: one is the fixed-probability threshold and the other is the age-dependent probability threshold [7]. Although fixed thresholds have been adopted in most countries, only the thresholds recommended by the National Osteoporosis Foundation (NOF) of the United States have rationale [8, 9]; 3% for hip fracture and 20% for a major osteoporotic fracture have been recommended as thresholds in China's latest guidelines [10, 11]. The age-dependent probability threshold, which was developed by the National Osteoporosis Guideline Group (NOGG) [12], is primarily used in the United Kingdom. Its intervention thresholds are equivalent to the risk associated with previous fractures in persons below the age of 70 years. As the risk of fracture increases with age, fixed thresholds are used at age 70 and above. Regardless of which threshold option is chosen, the FRAX® tool has a record of outstanding performance in predicting high-risk groups for fracture. However, the setting of the reference threshold should be country specific [7].

Given the aging of the Chinese population, the number of patients with osteoporosis is increasing, but the diagnosis and treatment rates remain low [11]. In China, the incidence of hip fracture among females is higher than among males [13]. Chinese women aged 50 years are at high risk for an osteoporosis-related fracture [14], and preliminary studies suggest that FRAX® predictions may underestimate the risk of fracture among Chinese postmenopausal women [15]. A cross-sectional study of elderly Chinese men, using the FRAX tool without BMD measurements, yielded inconclusive findings and uncertainty about the predictive value of FRAX for osteoporosis [16], while the diagnosis of osteoporosis using BMD measurements (T-score ≤ -2.5) is based on only one diagnostic criterion of the Chinese guidelines. Another study, which compared individuals with recent fractures and high-risk groups defined by FRAX calculation, reported that the NOF threshold identified less than half of the study participants as high risk for fracture before the fracture occurred [17]. No Chinese-specific recommendation for a FRAX®-based intervention threshold has been based on Chinese epidemiological data on the incidence of osteoporotic fractures and factors influencing them [11]. Previous studies based on FRAX found that low vitamin D levels were associated with increased fracture risk, and a high prevalence of vitamin D deficiency in postmenopausal Chinese women was confirmed [18], indicating that Chinese postmenopausal women may have a high risk of osteoporosis.

The aim of the present study was to judge which strategy (i.e., the NOF or NOGG thresholds) is more appropriate for use with the postmenopausal population of China using the FRAX® Chinese model and Chinese-specific intervention thresholds.

Materials and methods

Participants

Postmenopausal women over 50 years old ($N = 264$) were randomly recruited from community medical centers in Changsha City, Hunan Province, China, in September 2017. Menopause was defined as the absence of menstrual cycles for longer than 1 year. None of the participants was institutionalized and all were in good health, consciously, communicated, without limitation of activity. The use of antiosteoporosis medication was the only exclusion criterion. Standard medical assessment questionnaires were distributed to all participants to collect data on their medical, social and family histories, and clinical risk factors. These factors included a parental history of hip fracture, exposure to systemic glucocorticoids for more than 3 months, a history of fragility fracture, current smoking, high alcohol intake (3 or more units daily, on average), the presence of rheumatoid arthritis, and secondary

osteoporosis. Secondary osteoporosis factors included insulin-dependent (type 1) diabetes mellitus, adult osteogenesis deficiency, long-term untreated hyperthyroidism, hypogonadism or premature menopause (<45 years old), chronic malnutrition or malabsorption, and chronic liver disease. The study was conducted in accordance with Helsinki Declaration II and approved by the Ethics Committee of Xiangya Second Hospital, South China University, Changsha, China. Each participant provided written informed consent.

Methods

Current height was measured to the closest 0.5 cm, using a stadiometer mounted on a wall, by pressing a horizontal plate on the head and flattening the hair. Weight was measured using an electronic scale, to the closest 0.1 kg. Body mass index (BMI) was calculated by dividing the body weight by the height squared (kg/m^2). Participants' current age and age at menopause were self-reported. BMD was measured at the femoral neck using dual-energy X-ray absorptiometry (DXA; Discovery Wi S/N87556, Hologic, USA). The 10-year risk for a major osteoporotic fracture and the 10-year risk for osteoporotic hip fracture were calculated using the FRAX® model, and the *T*-score of the femoral neck was included in the calculations. Positive and lateral vertebral X-rays were taken to assess vertebral fractures and confirm the diagnosis of osteoporosis.

Bone mineral density measurements

An experienced doctor measured BMD at the lumbar spine, left femoral neck, and total hip using DXA. According to the manufacturer (Discovery Wi S/N87556, Hologic, USA), a daily controlled phantom scan of the spine showed a long-term (>2 years) coefficient of variation (CV) of less than 0.7%. Based on repetitive scanning, the CVs were 1.1% for the femoral neck, 0.9% for the total hip, and 1.2% for the lumbar spine. As recommended by the World Health Organization, osteoporosis was defined as a *T*-score ≤ −2.5, which was used in the BM reference databases established by our group [19].

Diagnosis of vertebral fractures

Vertebral fractures were assessed using X-ray imaging of the lateral spine from T4 to L4 (Uni-Vision 61Y040, Shimadzu, Japan). Using a visual semiquantitative method, fracture was defined as the ratio of the anterior to posterior or middle to posterior vertebral height <0.80, or the ratio of the posterior to posterior vertebral height compared with adjacent vertebra [20, 21].

Statistical analyses

Sample characteristics are presented as mean ± standard deviation for continuous variables. A receiver-operating characteristics (ROC) curve was generated and the area under the curve was calculated to determine the diagnosis of osteoporosis. The best cut-off point was estimated using the Youden index, and the accuracy of the thresholds was assessed by analyzing their sensitivity, specificity, predictive value, and likelihood ratios. All data management and analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL).

Results

Information on the characteristics of the 264 postmenopausal women that was extracted from the completed questionnaires is summarized in Table 1. The average age of the 264 respondents was 66.5 ± 9.0 years, and their age at menopause was 49.5 ± 3.7 years. Their mean weight and height were 56.0 ± 8.0 kg and 154.3 ± 5.7 cm, respectively, and their mean BMI was 23.5 ± 3.1. No patients with rheumatoid arthritis were included in the study. Individuals who were currently smoking or drinking accounted for a small proportion of participants and very few women had been treated with glucocorticoids. Individuals with secondary osteoporosis accounted for 13.5% of the sample.

According to China's guidelines for the diagnosis and treatment of primary osteoporosis, one of the following three criteria are required for a diagnosis of osteoporosis: (1) fragility fracture of the hip or spine; (2) *T*-score ≤ −2.5 based on DXA measurements of BMD of the medial axis

Table 1 Participants' characteristics and the prevalence (%) of clinical risk factors ($N = 264$)

Variables	
Number, *n*	264
Age, years	66.5 ± 9.0
Age at menopause, years	49.5 ± 3.7
Years since menopause, years	16.9 ± 9.6
Weight, kg	56.0 ± 8.0
Height, cm	154.3 ± 5.7
Body mass index, kg/m^2	23.5 ± 3.1
Rheumatoid arthritis, %	0
Smoking, %	1.5
Glucocorticoid use, %	2.3
Parental hip fracture, %	7.2
Prior fracture, %	8.0
Alcohol intake, %	3.0
Secondary osteoporosis, %	13.5

Table 2 Diagnosis of osteoporosis based on diagnostic criteria

Osteoporosis diagnostic criteria	Osteoporosis diagnosed
BMD (hip) ≤ −2.5	80
BMD (lumbar) ≤ −2.5	55
BMD (hip or lumbar) ≤ −2.5	91
Fragility fracture	28
Low bone mass with fragility fracture	8
Any criteria	92

BMD bone mineral density

Table 3 The 10-year probabilities for osteoporotic hip fracture and a major osteoporotic fracture calculated using FRAX (including BMD)

Age group	Number	10-year hip fracture probability (%)	10-year major osteoporotic fracture probability (%)
50–54	31	0.35 ± 0.31	2.53 ± 0.68
55–59	34	0.69 ± 0.66	3.48 ± 2.23
60–64	53	0.95 ± 0.88	4.33 ± 1.93
65–69	45	1.38 ± 1.06	4.88 ± 2.06
≥70	101	3.75 ± 2.83	7.82 ± 3.82
≥50	264	1.99 ± 2.34	5.44 ± 3.41

FRAX Fracture Risk Assessment, *BMD* bone mineral density

(lumbar spine 1–4, femoral neck, or total hip) or 1/3 of the distal radius; or (3) BMD measurements consistent with low bone mass ($-2.5 < T\text{-score} < 1.0$) accompanied by a fragility fracture of the proximal humerus, the pelvis, or the distal forearm [11]. A diagnosis of osteoporosis was confirmed in 92 participants in the cohort using the diagnostic criteria (Table 2), including 11 individuals who were diagnosed with secondary osteoporosis.

There were 28 participants who sustained fractures; 11 of them were lumbar vertebral fractures, 9 were thoracic vertebral fractures, 4 were combined lumbar vertebral fractures and thoracic vertebral fractures, and 4 were hip fractures. As shown in Table 3, the 10-year FRAX risks for both hip fracture and a major osteoporotic fracture increased with age (Table 3). The data were analyzed using two thresholds to compare participants identified as having a high risk for fracture and actual patients with osteoporosis (Table 4). Compared to the NOGG threshold, more participants with a high risk for fracture were identified using the NOF threshold, and the number of participants identified was closer to the number of patients with osteoporosis.

To ascertain which of the thresholds (i.e., the threshold recommended by the NOGG or the NOF) was more suitable for use with Chinese postmenopausal women, their sensitivity and specificity were evaluated (Table 5). Taking an osteoporosis diagnosis as the gold standard, the sensitivity and specificity were 91.38% and 81.07%, respectively,

Table 4 Comparison of the results using the thresholds recommended by the NOF and NOGG (including BMD)

Age group	Number	Osteoporosis	NOF	NOGG
50–54	31	0	0	0
55–59	34	5	0	1
60–64	53	11	2	2
65–69	45	15	3	3
≥70	101	61	53	18
≥50	264	92	58	24

NOF National Osteoporosis Foundation, *NOGG* National Osteoporosis Guideline Group, *BMD* bone mineral density

Table 5 Sensitivity, specificity, accuracy, and positive and negative likelihood ratios of the NOF and NOGG thresholds

	NOF	NOGG
Sensitivity	91.38%	100%
Specificity	81.07%	71.67%
Accuracy	83.33%	74.24%
Positive likelihood ratio	4.83	3.52
Negative likelihood ratio	0.11	0

NOF National Osteoporosis Foundation, *NOGG* National Osteoporosis Guideline Group

using the NOF thresholds, and 100% and 71.67%, respectively, using the NOGG thresholds. The accuracy of the NOF strategy was 83.33% and it was 74.24% for the NOGG strategy. The positive and negative likelihood ratios of the NOF thresholds were 4.83 and 3.52, respectively, and they were 0.11 and 0, respectively, for the NOGG thresholds.

The ROC was analyzed to determine the optimal threshold applicable to Chinese postmenopausal women. The area under the ROC curve was 0.937 for the 10-year probability of hip fracture, while the cut-off point was 2.05 (Fig. 1), the area under the ROC curve was 0.938 for the 10-year probability of a major osteoporotic fracture, and the cut-off point was 5.55 (Fig. 2).

Discussion

The present study showed 34.8% of postmenopausal women were diagnosed with osteoporosis, indicating that a substantial proportion of Chinese postmenopausal women have this serious health problem. However, the thresholds for the Chinese population were uncertain owing to the absence of health-related economic and epidemiological data that most studies, including the Chinese guideline for the Chinese FRAX®, used to develop the thresholds recommended by the NOF (i.e., economic data from America), which was reasonable. Previous studies have

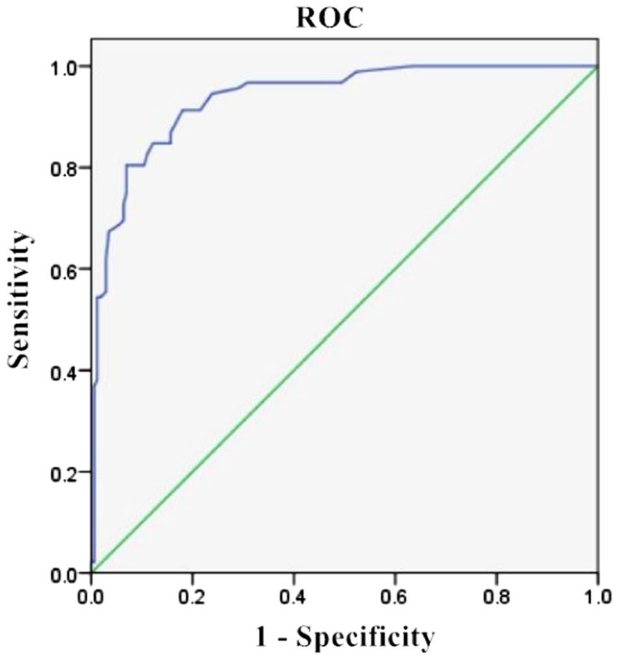

Fig. 1 ROC curve of the 10-year risk for hip fracture. ROC receiver-operating characteristics

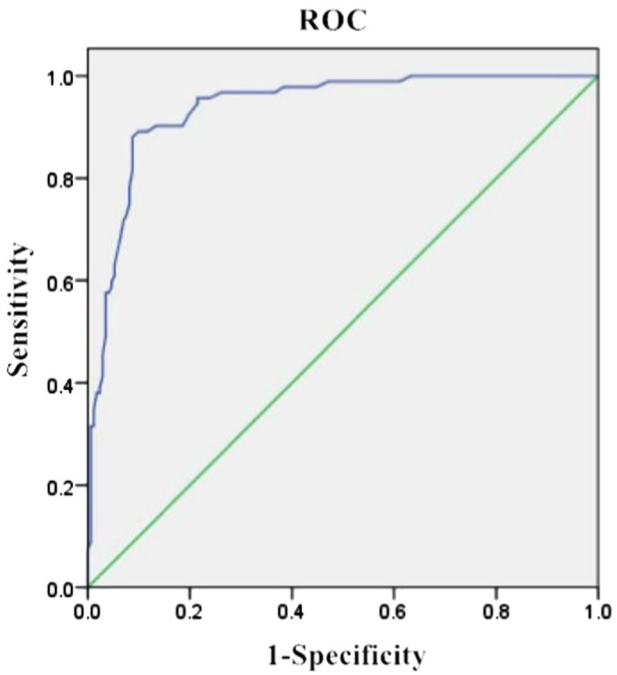

Fig. 2 ROC curve of the 10-year risk for a major osteoporotic fracture. ROC receiver-operating characteristics

questioned the reliability of the FRAX instrument in predicting the risk of fracture among postmenopausal women because of the obvious flaw that it does not consider increases in fracture risk proportional to increases in age [15]. In 2013, the FRAX manufacturer released an updated model for China, which corrected the trends in fracture risk with age. The latest version of the FRAX instrument should be re-evaluated for use with Chinese postmenopausal women.

The results suggested that fracture risk calculated using FRAX increased with age, which is consistent with the results of another study, in which age was a risk factor in the FRAX algorithm [22]. In the current study, more participants were classified as having a high risk for fracture with increased age, regardless of whether the NOGG or NOF strategies were used. The results showed 58 women as at high risk using the NOF thresholds and 24 using the NOGG thresholds, indicating that the number of participants identified as being at risk using the NOF was closer to the number of participants (92) diagnosed with osteoporosis. When the participants were <70 years old, the NOF and NOGG thresholds had similar discriminant ability, but when they were ≥70 years old, the NOF thresholds performed remarkably better than the NOGG thresholds (53 versus 18 women), with the difference explained mainly by the difference in the 10-year risk for hip fracture. As in other studies, the 10-year probability of hip fracture was more accurate than the 10-year probability of a major osteoporotic fracture [17]. The mean 10-year hip fracture risk was 3.75 ± 2.83, which exceeded the 3% thresholds of the NOF but fell behind the 5.4% fixed thresholds of the NOGG. It seems that the 10-year probability of hip fracture surpassed the 10-year probability of a major fracture in predicting actual fragile fractures [17]. Based on our study, the main difference between the NOGG and the NOF screenings of women ≥70 years old was whether they had a prior fracture.

The differences between the effects of NOF strategies and NOGG strategies on secondary osteoporosis were proved by NOF schemes showing higher accuracy than NOGG schemes; however, the very limited sample of secondary osteoporosis questioned the reliability.

Although the screened number of NOGG thresholds was lower than the number of NOF thresholds, the sensitivity reached 100%, while the sensitivity of the NOF thresholds was 91.38%. The specificity of the NOF thresholds was 81.07%, and it was 71.67% for the NOGG thresholds. When choosing the recommendation with extremely high sensitivity, such as the NOGG strategy, the rate of missed diagnoses was low; however, the specificity was relatively poor, which was related to the high rate of misdiagnoses. The comparison of the NOGG and NOF strategies revealed the accuracy of the NOF thresholds was superior to that of NOGG thresholds, showing high sensitivity and specificity without extreme values, thereby achieving a balance between the rates of missed diagnoses and misdiagnoses. Thus, this study was able to identify individuals with a high risk for osteoporosis using the China's FRAX model. The results showed that the fixed threshold was more

appropriate for the Chinese population. The suitability of the NOF thresholds for Chinese individuals may be related to the estimated residual life risk for fractures among Chinese women ≥50 years old and its similarity to the residual life risk for fractures among white women in America ≥50 years old [23]. The ROC curves were analyzed to identify Chinese-specific thresholds and determine whether fixed thresholds were better. The area under the curve for detecting osteoporosis using the 10-year risk for major osteoporosis fracture was 0.938 and the cut-off point was 5.55, while the area under the curve for detecting osteoporosis using the 10-year risk for hip osteoporosis fracture was 0.937 and the cut-off point was 2.05. Both hip and major osteoporotic fracture risks were lower than the American thresholds, but had higher sensitivity and specificity, and the cut-off points were recommended as Chinese thresholds. Currently, little is known about osteoporosis and its complications in China [24]. The medical gap between urban and rural areas might require relatively lower thresholds for early screening of osteoporosis.

It was also confirmed that NOF thresholds were superior to NOGG thresholds when FRAX was calculated without *T*-score, even though the sensitivity and accuracy of both NOF schemes and NOGG schemes decreased compared to those with BMD, considering the diagnosis of osteoporosis as the gold standard (data unpublished). On the basis of diagnostic criteria for osteoporosis in as defined by Chinese guidelines, which include the BMD results, only FRAX calculation with *T*-score was included in the present analysis.

This study has several limitations. First, the sample size was small. Second, FRAX was used to predict the 10-year fracture risk, but there was no follow-up period; therefore, a comprehensive evaluation of the application of FRAX in China was not possible. Third, the bone mass of participants predisposed to fragility fractures was low ($-2.5 < T\text{-score} \leq -1$), indicating that fractures had occurred before osteoporosis was diagnosed, while we used the diagnosis of osteoporosis as a criterion for evaluation.

Conclusion

The NOF thresholds outperformed the NOGG thresholds in the detection of osteoporosis in Chinese postmenopausal women. The NOF thresholds predicted osteoporosis in Chinese postmenopausal women based on the latest FRAX® China model. The fixed thresholds were more appropriate for use in China: the recommended screening threshold for the 10-year risk of a major osteoporosis fracture was 5.55 and it was 2.05 for the 10-year risk of osteoporosis hip fracture among Chinese postmenopausal women.

Funding This work was supported by grants from the National Nature Science Foundation of China [grant numbers 81471091 and 81870622] and the Hunan Nature Science Foundation [grant number 2018JJ2574].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All research procedures in this study were in accordance with the ethical standards of institutions and with the 1964 Helsinki declaration and its subsequent amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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