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ORIGINAL ARTICLE

Setting the new FRAX reference threshold without bone mineral density in Chinese postmenopausal women

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Abstract

Purpose Despite the large number of osteoporosis patients in China, the diagnosis and treatment rates remain low. The Fracture Risk Assessment Tool (FRAX) can be used to effectively evaluate fracture risk. In this study, we explored the Chinese-specific thresholds of FRAX without the T-score.

Methods In all, 264 postmenopausal women aged > 50 years were randomly recruited from community-medical centers. All subjects completed self-reported questionnaires, BMD measurements, and spinal radiographs. The 10-year hip and major osteoporotic fracture risks were calculated by FRAX. A new threshold for both 10-year hip and major osteoporotic fracture risk was explored with receiver operating characteristic (ROC) curve analysis.

Results Overall, 92 subjects were diagnosed with osteoporosis. Among them, 14 participants with T-score > −2.5 were diagnosed with osteoporosis based on clinical fractures. ROC analysis showed the cut-off value of the 10-year hip osteoporotic fracture for detecting osteoporosis was 0.95%, while that of 10-year major osteoporotic fracture was 4.95%. The sensitivity and specificity of the 10-year hip osteoporotic fracture probability for detecting osteoporosis were 0.86 and 0.59, respectively, while the guideline-recommended threshold had a sensitivity of 0.49 and specificity of 0.83. The sensitivity and specificity of the 10-year major osteoporotic fractures with the new threshold were 0.76 and 0.69, respectively, while the recommended threshold had a sensitivity of 0 and specificity of 1.

Conclusion Current guideline-recommended FRAX thresholds without BMD showed low sensitivity. Therefore, 10-year osteoporotic hip fracture probability ≥ 0.95% and 10-year osteoporotic major fracture probability ≥ 4.95% are recommended as the new thresholds.

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

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Introduction

Osteoporosis is defined as a disorder of the skeletal system characterized by reduced bone strength and increased risk of fracture [1]. Osteoporosis and osteoporosis-related fracture have become a common public health concern, especially in the case of hip or spine fractures which can have devastating consequences [2]. It was estimated in 2015 that the incidence of osteoporotic fractures (wrist, vertebra, and hip) in China were 2.69 million in 2015 and is projected to be approximately 4.83 million by 2035 and 5.99 million by 2050 [3]. The risk of osteoporotic fractures in women (40%) was higher than the risks of breast, endometrial, and ovarian cancer combined [4], and was approximately three times higher than in men [3]. The main management approach is to prevent osteoporotic fractures and provide timely treatment for patients with high fracture risk. However, the challenge remains to accurately define and identify people with high fracture risk.

The United States Prevention Services Task Force (USPSTF) recommends that postmenopausal women aged > 65 years should undergo dual energy X-ray absorptiometry (DXA) to measure the bone mineral density (BMD), while for postmenopausal women aged < 65 years, DXA should be performed after Fracture Risk Assessment Tool (FRAX) assessment [5]. The FRAX tool—an osteoporosis risk assessment test—was developed by University of Sheffield in 2008 to evaluate high fracture risk online (www.shef.ac.uk/FRAX) [6]. FRAX calculation takes age, sex, weight, height, previous fracture, parent fractured hip, current smoking, glucocorticoids, and rheumatoid arthritis, with or without BMD, into consideration to assess osteoporotic fracture risk. There are two main detecting thresholds: one is the fixed threshold recommended by the National Osteoporosis Foundation (NOF), with 20% major osteoporotic fracture or 3% hip fracture risk [7], which is also adopted by the Chinese guideline [8]; the other is age-related increasing threshold applied by the National Osteoporosis Guideline Group (NOGG) before patient age of 70 years. When patient age exceeds 70 years, the fixed threshold is adopted [9]. In our early study, it was confirmed that fixed threshold was more appropriate for fracture risk assessment in Chinese postmenopausal women [10].

With the increase in the aging population, the number of patients with osteoporosis in China is also increasing. However, despite this, the rate of diagnosis and treatment remains low [8]. With a potentially large osteoporosis population in China, especially postmenopausal women, it is urgent to identify individuals at high risk for early diagnosis and timely treatment. Owing to the gap between rural and urban medical conditions in China, it is uncertain whether DXA can be consistently processed for all patients [11]. FRAX is advantageous in that it is convenient and economical to employ, and is hence worthy of promoting widely in China. However, there is no specific Chinese recommendation for FRAX intervention thresholds based on updated Chinese epidemiological data of fracture incidence and its influencing factors [8]. In the NOF, NOGG, and Chinese guidelines, there is no threshold distinction between the addition or elimination of BMD. In our previous study, we investigated in setting FRAX thresholds with BMD in Chinese postmenopausal women [10]. In this study, we developed a novel approach to establish FRAX risk assessment threshold without BMD to identify patients with high fracture risk among Chinese postmenopausal women.

Methods

Participants

Postmenopausal women aged over 50 years ($N = 264$) were randomly enrolled from community medical centers in Changsha City, Hunan Province, China in September 2017. Menopause is defined as having no menstrual cycle for more than a year. The only exclusion criterion was a history of anti-osteoporotic medication. All participants completed the standard medical assessment questionnaires by themselves, which contained their medical, social and family histories and clinical risk factors. The fracture risk factors were parental hip fracture history, systemic treatment with glucocorticoids for more than 3 months, fragility fracture history, current smoking status in the past half year, high alcohol consumption (on average more than 3 units/day), rheumatoid arthritis, and secondary osteoporosis. Secondary osteoporosis factors were type 1 diabetes mellitus, osteogenesis imperfecta in adults, long-term untreated hyperthyroidism, hypogonadism or menopause under 45 years, chronic malnutrition, chronic malabsorption, and chronic liver disease. The study was conducted in accordance with the tenets of Helsinki Declaration II and was approved by the Ethics Committee of Xiangya Second Hospital, South China University, Changsha, China. Written informed consent was provided by each participant.

Measurement

Patient height was measured using a wall-mounted sight gauge by pressing the horizontal plate on the head and flattening the hair, to the nearest 0.5 cm. Weight was measured to the closest 0.1 kg with an electronic scale. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). Participants' self-reported current

age and age at menopause were recorded. BMD was measured by DXA (Discovery Wi S/N87556, Hologic, USA). The 10-year risk for major osteoporotic fractures and 10-year risk for osteoporotic hip fractures were calculated by the FRAX model (modified Chinese version). Lateral thoracic and lumbar spine radiographs were used for diagnosing vertebral fractures and assisting the diagnosis of osteoporosis.

Bone mineral density measurements

The BMD of the lumbar spine, left femoral neck, and total hip were measured by an experienced doctor. Daily controlled phantom scans of the spine showed that the long-term (> 2 years) coefficient of variation (CV) was less than 0.7%, according to the manufacturer [12]. On the basis of repetitive scanning, the CVs of the femoral neck, total hip, and lumbar spine were 1.1%, 0.9%, and 1.2%, respectively.

Diagnosis of vertebral fractures

Vertebral fractures were assessed using radiographic imaging of the lateral spine from T4 to L4 (Uni-Vision 61Y040, Shimadzu, Japan). Using a visual semi-quantitative 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 the adjacent vertebra [13, 14].

Diagnosis of osteoporosis

The guidelines for diagnosis and treatment of primary osteoporosis in China were updated in 2017. The criteria for diagnosis of osteoporosis were as follows: (1) fragility fractures of the hip or vertebra; (2) T-score of DXA measurement of BMD in the medial axial skeleton (L1–L4, femoral neck, and total hip) or one-third of the distal radius was less than − 2.5; and (3) BMD results were in accordance with low bone mass (− 2.5 < T-score < 1.0) with fragile fractures of the proximal humerus, pelvis, or distal forearm [8]. Osteoporosis could be diagnosed when any of the above criteria was met.

Statistical analyses

The ROC curve was plotted and the area under the curve (AUC) was calculated to aid in the detection of osteoporosis diagnosis. The cut-off value was estimated by the Youden index, and its accuracy was assessed by the sensitivity, specificity, and likelihood ratios. All data analysis and management were executed by SPSS 17.0 software (SPSS Inc., Chicago, IL).

Results

In all, 264 postmenopausal women were included. Their basic demographic and clinical characteristics were refined from questionnaires. The age range of the patients was 50–85 years. The range of menopause age was from 35 to 58 years, and the years since menopause ranged from 1 to 42 years. The weight range was 34.8–82.6 kg, and the height range was 135.0–169.3 cm. The BMI varied from 15.26 to 34.75 kg/m^2. No patient had a history of rheumatoid arthritis in this study. Only four participants were current smokers and eight subjects were current alcohol drinkers. Parental hip fracture history was confirmed in 19 subjects, prior fracture history was found in 21 individuals, and secondary osteoporosis was diagnosed in 33 postmenopausal women.

In the study, 92 individuals were diagnosed as osteoporosis. Participants were classified by T-score: T-score ≥ − 1.0, − 2.5 < T-score < 1.0, and T-score < − 2.5 group. In T-score ≥ − 1.0 group, one of 47 individuals were diagnosed as having osteoporosis, while three people were found with 10-year hip osteoporotic fracture risk ≥ 3%, and no participants had major osteoporotic fracture ≥ 20%. In the 2.5 < T-score < 1.0 group, 13 of 139 postmenopausal women were diagnosed with osteoporosis, 32 women were noted to have 10-year hip osteoporotic fracture risk ≥ 3%, and no patients had major osteoporotic fracture risk ≥ 20%. In T-score ≤ -2.5 group, all patients had confirmed osteoporosis, 39 of 78 subjects were 10-year hip osteoporotic fracture risk ≥ 3%, and no one had major osteoporotic fracture risk ≥ 20%.

ROC analysis was used to determine the optimal threshold for Chinese postmenopausal women. The area under the ROC curve of the 10-year hip osteoporotic fracture was 0.783, and the cut-off point was 0.95 (Fig. 1a). The area under the ROC curve of the 10-year major osteoporotic fracture was 0.784, and the cut-off point was 4.95 (Fig. 1b). The sensitivity of the 10-year hip fracture probability ≥ 0.95% and of guideline-recommended thresholds for detecting osteoporosis were 0.86 and 0.49, respectively. The specificity of new thresholds and of recommended thresholds for screening osteoporosis were 0.59 and 0.83, respectively (Table 1). Both positive and negative likelihood ratios of new thresholds were lower than those of guideline thresholds. Meanwhile, the sensitivity of 10-year major osteoporotic fracture probability ≥ 4.95% and guideline-recommended thresholds for detecting osteoporosis were 0.76 and 0, respectively. The specificity of new thresholds and of recommended thresholds for screening osteoporosis were 0.69 and 1, respectively. The negative likelihood ratios of new thresholds was lower than those of recommended thresholds (Table 2).

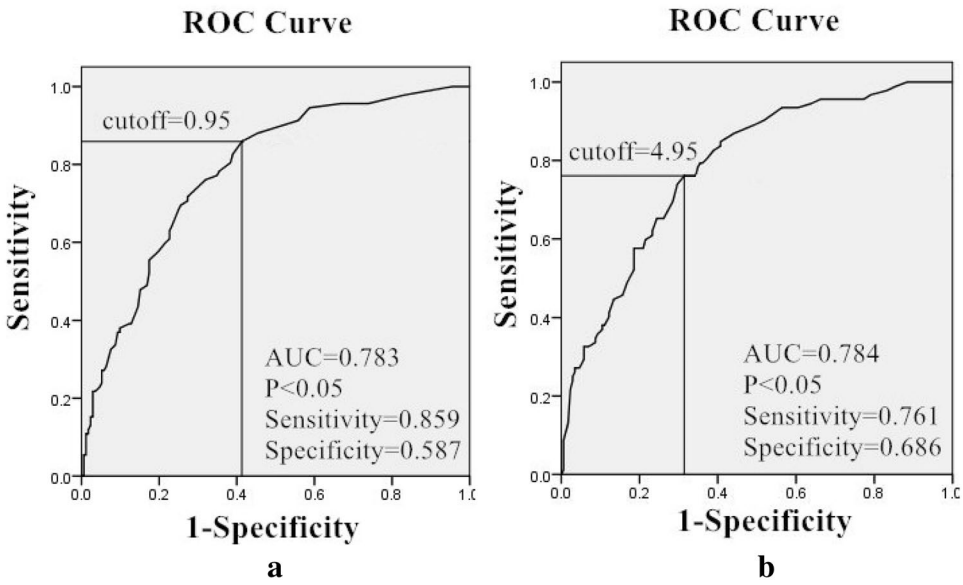

Fig. 1 **a** ROC of 10-year hip osteoporotic fracture risk (cut-off value = 0.95); **b** ROC of 10-year major osteoporotic fracture risk (cut-off value = 4.95)

Table 1 Comparison between the guideline-recommended threshold and new threshold of 10-year hip fracture probability

	10-year hip fracture probability ≥ 3%	10-year hip fracture probability ≥ 0.95%
Sensitivity	0.49	0.86
Specificity	0.83	0.59
Positive likelihood ratio	2.90	2.08
Negative likelihood ratio	0.61	0.24

Discussion

In this study, we found that the prevalence of osteoporosis among Chinese postmenopausal women was very high, which indicates that a large population of patients suffer from osteoporosis and osteoporosis-related fractures [15, 16]. BMD measurement is not widely used in China, which leads to delayed assessment of patients' bone health status. However, assessment based on BMD showed relatively low sensitivity to detect high fracture risk in people, as the majority of fragile fractures occur when T-score > − 2.5, which was not in accordance with diagnosis of osteoporosis by BMD [17]. Thus, using the FRAX assessment tool evaluates osteoporotic fracture risk without BMD results and is hence important for risk identification.

There were no differences in the guideline-recommended thresholds between with and without BMD measurement. Several studies have proven that FRAX evaluation with T-score is more efficient than without it [18, 19]. Therefore, exploring appropriate thresholds without BMD measurement is essential for a Chinese-specific population.

In all, 92 subjects were diagnosed with osteoporosis. Among them, 14 patients mainly with T-score > − 2.5 were diagnosed with osteoporosis based on either previous fragile fracture in a specific bone site or radiographically determined vertebral fracture. This indicated that patients with osteopenia with fragile fractures who require early treatment would go undetected if only BMD-defined osteoporosis was used as the diagnostic criterion.

The osteoporosis-detecting ability was completely different between the guideline-recommended thresholds of the 10-year hip fracture probability ≥ 3% and the 10-year major osteoporotic fracture probability ≥ 20%, in that the latter showed poor performance. However, when predicting actual fragile fractures, the 10-year probability of hip fractures seemed to exceed the 10-year probability of major fractures in terms of accuracy [20]. Overall, 39 of 78 patients with BMD-defined osteoporosis were detected by FRAX,

Table 2 Comparison between the guideline-recommended threshold and new threshold of 10-year major osteoporotic fracture probability

	10-year major osteoporotic fracture probability ≥ 20%	10-year major osteoporotic fracture probability ≥ 4.95%
Sensitivity	0	0.76
Specificity	1	0.69
Positive likelihood ratio	–	2.42
Negative likelihood ratio	1	0.35

32 patients with osteopenia were filtered by FRAX, and five were diagnosed as having osteoporosis. The results showed that insufficient sensitivity of reference thresholds required re-evaluation.

New thresholds were calculated through ROC curve analysis. Compared to the guideline thresholds, the sensitivity increased by new thresholds showed that the 10-year hip fracture probability was ≥ 0.95%, while the specificity decreased. The sensitivity of the new threshold is much greater than that recommended in the guideline. Thus, the threshold used for screening can screen more people. Even though the specificity was relatively low when using new thresholds, the majority of osteoporosis cases (70/92) could be detected. Moreover, as little awareness of osteoporosis and its risks comprise the current situation in China [21], the potential osteoporosis risk population should be identified as much as possible. Even though the specificity does not substantiate the numbers of osteopenic subjects without osteoporosis diagnosis that would be included, the most probable individuals for osteoporotic fracture were masked by osteopenia instead of osteoporosis. Considering the inconsistency in medical care in China, a threshold with higher sensitivity was more recommendable.

The extremely low sensitivity and high specificity of the recommended 10-year major osteoporotic fracture thresholds limit the screening ability of the threshold. High sensitivity of new thresholds that the 10-year major osteoporotic fracture probability ≥ 4.95% provides better screening efficiency. Although the specificity of the new threshold is lower than that of the guideline-recommended thresholds, it still shows relatively high specificity. Thus, the new threshold can be used for diagnostic screening. According to the positive and negative likelihood ratios, new thresholds also showed better detection ability. Therefore, it is more suitable to adopt the new threshold.

This study has some limitations. First, the subject sample size was relatively small. Second, the collection of medical history such as risk factors and previous fractures is based on self-administered questionnaires, which may cause recall bias and reporting bias. Third, BMD measurements of distal radius were not included. Fourth, the follow-up period of new occurrence of fractures was missing. Finally, other fracture risk factors such as falls were not considered.

Conclusion

The current guideline-recommended FRAX thresholds without BMD showed low sensitivity in detecting osteoporosis in Chinese postmenopausal women. The 10-year osteoporotic hip fracture probability ≥ 0.95% and 10-year osteoporotic major fracture probability ≥ 4.95% are the newly recommended thresholds that require BMD testing or medical treatment when the threshold was exceeded.

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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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