Postprint: Predictive Value of FRAX for Fracture Risk and Intervention Thresholds in Beijing Residents

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Abstract

Background: In China, the overall diagnosis and treatment rate for osteoporotic fractures is relatively low, necessitating the identification of reliable predictive tools. FRAX is recommended by China's osteoporosis diagnosis and treatment guidelines, yet its predictive value and intervention thresholds in the Mainland Chinese population require further validation.

Objective: To evaluate the predictive value of FRAX for fracture risk among Beijing residents and to explore intervention thresholds.

Methods: From 2011–2012, 1018 participants were recruited from four community health service centers in Beijing. The 10-year risk of major osteoporotic fracture (MOF) and hip fracture (HF) for each participant was calculated using FRAX. Participants were followed up from 2021–2022 to obtain self-reported fracture incidence over the 10-year period. Using actual fracture occurrence as the "gold standard," receiver operating characteristic (ROC) curves for FRAX prediction were plotted and area under the curve (AUC) was calculated to evaluate FRAX's fracture risk predictive value for Beijing residents and to explore intervention thresholds.

Results: A total of 469 participants (46.07%) were successfully followed up. The median MOF probability calculated by FRAX was 2.6% (2.2%, 3.7%), and the median HF probability was 0.5% (0.3%, 0.9%). Forty-nine participants (10.45%) experienced MOF during the 10-year period, of which 5 (1.07%) were HF. ROC curve analysis revealed that the AUCs for FRAX and femoral neck bone mineral density (BMD) alone in predicting MOF were 0.683 and 0.662, respectively. The cutoff value at the maximum Youden's index was 2.95%, with a sensitivity of 59.2% and specificity of 67.6%.

Conclusion: FRAX demonstrates moderate predictive ability for future fractures, though improvement is needed. A predicted MOF probability of 2.95% represents the cutoff value at maximum Youden's index and may serve as a reference for establishing intervention thresholds.

Full Text

The Discriminative Ability of FRAX and Possible FRAX-based Intervention Thresholds for Beijing-dwelling People

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Abstract

Background: The overall diagnosis and treatment rate of osteoporotic fractures is low in China, creating an urgent need for reliable prediction tools. Although FRAX is recommended in Chinese osteoporosis guidelines, its predictive value and appropriate intervention thresholds for mainland Chinese populations require further validation.

Objective: To evaluate the predictive value of FRAX for fracture risk in Beijing residents and explore potential intervention thresholds.

Methods: A total of 1,018 participants were recruited from four community health service centers in Beijing between 2011 and 2012. The 10-year probabilities of major osteoporotic fracture (MOF) and hip fracture (HF) were calculated for each participant using FRAX. Follow-up surveys conducted in 2021–2022 collected self-reported fracture data over the 10-year period. Using actual fracture occurrence as the gold standard, receiver operating characteristic (ROC) curves were constructed and area under the curve (AUC) values were calculated to evaluate FRAX predictive performance and identify optimal intervention thresholds.

Results: Of the original cohort, 469 participants (46.07%) were successfully followed up. The median FRAX-calculated MOF probability was 2.6% (IQR: 2.2%, 3.7%), and the median HF probability was 0.5% (IQR: 0.3%, 0.9%). During the 10-year follow-up period, 49 participants (10.45%) experienced MOF,

including 5 cases (1.07%) of HF. ROC analysis revealed AUC values of 0.683 for FRAX and 0.662 for femoral neck bone mineral density (BMD) alone in predicting MOF. The optimal cutoff value based on maximum Youden's index was 2.95% MOF probability, with sensitivity of 59.2% and specificity of 67.6%.

Conclusion: FRAX demonstrates moderate predictive ability for future fractures in this population, though room for improvement remains. An MOF probability of 2.95% represents the optimal cutoff with maximum Youden's index and may serve as a reference for establishing intervention thresholds.

Key words: Fracture risk assessment tool; Osteoporotic fractures; Intervention thresholds; Diagnostic test

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Introduction

Osteoporotic fractures, also known as fragility fractures, occur during daily activities or with minimal trauma and represent severe complications of osteoporosis. It is estimated that by 2035, approximately 4.83 million osteoporotic fractures will occur annually in China, rising to 5.99 million cases by 2050, with associated annual expenditures reaching $25.43 billion [1]. Despite this substantial burden, the overall diagnosis and treatment rate for osteoporotic fractures remains low, with most high-risk patients not receiving effective therapy [2-3]. While bone mineral density (BMD) measurement is one method for assessing fracture risk, its predictive sensitivity is limited [4-7], highlighting the urgent need for more reliable risk prediction methods.

In 2008, the University of Sheffield launched the Fracture Risk Assessment Tool (FRAX) to estimate an individual's 10-year probability of major osteoporotic fracture (MOF, including hip, spine, wrist, and shoulder) and hip fracture (HF). FRAX can be used with or without BMD data. Chinese osteoporosis guidelines recommend this tool with U.S.-derived thresholds (MOF 20% or HF 3% to identify high-risk individuals) [2]. However, given variations in osteoporosis prevalence, healthcare systems, and cost-effectiveness across populations, country-specific thresholds are needed [8]. Currently, China lacks studies evaluating FRAX's predictive value using real 10-year fracture data from mainland populations and has not established population-specific intervention thresholds. This study addresses this gap by using actual 10-year fracture incidence as the gold standard to assess FRAX's predictive value in Beijing residents and explore potential intervention thresholds.

Methods

Study Participants Between 2011 and 2012, 1,018 eligible participants were recruited from four community health service centers in Beijing (Yuetan, Tiantan, Guangnei, and Shuangyushu). Inclusion criteria were: (1) age 40–90

years, and (2) no history of anti-osteoporosis medication. Exclusion criteria included inability to complete questionnaires or undergo BMD and X-ray examinations. The study was approved by the Ethics Committee of Fuxing Hospital Affiliated to Capital Medical University, and all participants provided informed consent.

FRAX Assessment Upon enrollment, participants completed a comprehensive questionnaire covering all FRAX risk factors: age, sex, weight, height, prior fracture history (timing, site, and cause), parental hip fracture history, smoking status (daily consumption, duration, and cessation), glucocorticoid use (medication name and dosage), rheumatoid arthritis, secondary osteoporosis conditions (type 1 diabetes, osteogenesis imperfecta, untreated hyperthyroidism, hypogonadism or menopause before age 45, chronic malnutrition/malabsorption, chronic liver disease), and alcohol consumption (daily intake and type, with 3 units considered heavy drinking, equivalent to ~285 mL beer, 120 mL wine, or 30 mL spirits). Participants also underwent dual-energy X-ray femoral neck BMD measurement and thoracolumbar spine X-rays to identify vertebral fractures. Researchers then entered all collected risk factors and femoral neck BMD T-scores into the official FRAX website (https://frax.shef.ac.uk/FRAX/) to obtain each participant's 10-year MOF and HF probabilities.

Follow-up Survey Between 2021 and 2022 (10 years after baseline), researchers conducted telephone follow-up surveys using a structured questionnaire covering demographic information and self-reported fracture events during the intervening decade (timing, cause, and site). Participants who could not be contacted after 3 attempts, refused participation, or were unable to participate due to Alzheimer's disease or death were classified as lost to follow-up.

Statistical Analysis Data were analyzed using SPSS 20.0 software. Categorical variables are presented as frequencies and percentages, with between-group comparisons using chi-square tests. Normally distributed continuous variables are expressed as means ±standard deviations and compared using t-tests. Non-normally distributed variables are presented as medians (P25, P75) and compared using Wilcoxon rank-sum tests. Using actual 10-year fracture occurrence as the gold standard, receiver operating characteristic (ROC) curves were constructed and area under the curve (AUC) values were calculated to evaluate the predictive performance of FRAX and femoral neck BMD T-scores for MOF and HF. Statistical significance was set at $P<0.05$.

Results

Baseline Characteristics The 1,018 participants at baseline had a median age of 61 years (IQR: 55, 70), with 151 males (14.83%) and 867 females (85.17%).

Median weight was 62 kg (IQR: 56, 70), median height was 160 cm (IQR: 156, 170), 188 (18.47%) had prior fracture history, 98 (9.63%) had parental hip fracture history, 56 (5.50%) were smokers, 23 (2.26%) used glucocorticoids, 13 (1.28%) had rheumatoid arthritis, 119 (11.69%) had secondary osteoporosis, and 24 (2.36%) were heavy drinkers. The median femoral neck BMD T-score was -1.9 (IQR: -2.6, -1.1). Based on BMD results, 311 participants (30.55%) were diagnosed with osteoporosis. The median FRAX-calculated MOF probability was 2.5% (IQR: 2.1%, 3.6%), and the median HF probability was 0.5% (IQR: 0.3%, 0.9%).

Comparison Between Followed and Lost-to-Follow-up Participants A total of 549 participants (53.93%) were lost to follow-up: 387 (70.49%) due to loss of contact, 131 (23.86%) who refused participation, and 31 (5.65%) due to Alzheimer's disease or death. The 469 successfully followed participants (46.07% retention rate) differed significantly from those lost to follow-up in age and FRAX-calculated MOF and HF probabilities ($P<0.05$), but showed no significant differences in weight, height, BMI, prior fracture history, parental hip fracture history, smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, osteoporosis diagnosis, heavy drinking, or femoral neck BMD T-scores ($P>0.05$) .

Fracture Incidence During Follow-up Among the 469 followed participants, 49 (10.45%) experienced MOF during the 10-year period, including 5 cases (1.07%) of HF. Specific fracture sites included distal forearm (n=20, 4.26%), vertebral (n=15, 3.20%), and upper arm (n=9, 1.92%). The 5 participants with HF had a median age of 60 years (IQR: 60, 67), mean weight of 61.6±8.3 kg, mean height of 159.4±6.3 cm, mean BMI of 24.2±2.3 kg/m^{2}, mean femoral neck BMD T-score of -2.0±1.1, mean FRAX-calculated MOF probability of 6.0±5.0%, and median HF probability of 1.0% (IQR: 0.6%, 3.6%). Three of these 5 participants had prior osteoporotic fracture history, and one each had rheumatoid arthritis, systemic glucocorticoid use, and secondary osteoporosis; none had parental hip fracture history, smoking history, or heavy drinking.

Comparison of Participants With and Without Incident Fractures Participants who experienced MOF differed significantly from those who did not in age, height, prior fracture history, osteoporosis history, femoral neck BMD T-scores, and FRAX-calculated MOF and HF probabilities ($P<0.05$). No significant differences were observed in weight, BMI, parental hip fracture history, smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, or heavy drinking .

Predictive Performance of FRAX for MOF Using actual fracture occurrence as the gold standard, ROC curves were constructed for FRAX and femoral neck BMD T-scores in predicting MOF. FRAX achieved an AUC of

0.683, compared to 0.662 for BMD alone. To balance sensitivity and specificity, the cutoff corresponding to maximum Youden's index was identified. At an FRAX-calculated MOF probability of 2.95%, Youden's index was maximized, yielding sensitivity of 59.2% and specificity of 67.6% [Figure 1: see original paper].

When applying the currently recommended intervention threshold (MOF 20% or HF 3%), only 4 of the 49 MOF cases had HF probability >3%, and none had MOF probability >20%. This threshold achieved sensitivity of only 8.2% but specificity of 98.6%.

Discussion

Despite China's large osteoporosis patient population, most remain undiagnosed and untreated. A national cross-sectional study found that among Chinese women 40 years, osteoporosis prevalence was 20.6%, vertebral fracture prevalence was 9.7%, and 4.2% had experienced a clinical fracture within 5 years, yet only 1.4% received anti-osteoporosis medication [3]. Limited BMD equipment, particularly in rural areas, contributes to this treatment gap [9]. FRAX offers an advantage by predicting fracture risk using readily available clinical risk factors without requiring BMD testing. While widely studied internationally, FRAX application in China remains in its early stages.

In this study, the 10-year MOF incidence was 10.45% and HF incidence was 1.07% among followed participants—higher than reported in studies from Hong Kong [10] and Japan [11] but similar to another Hong Kong cohort study [12]. Cheung et al. [10] followed 2,266 postmenopausal women for 4.5 years, observing MOF in 4.7% and HF in 0.9%. Tamaki et al. [11] reported 5.3% MOF and 0.5% HF in Japanese women over 10 years. Su et al. [12] found 6.6% of men and 11.0% of women 65 years in Hong Kong experienced at least one MOF over 9.94 and 8.82 years, respectively. As China's population ages, osteoporosis and fracture prevalence will continue rising, imposing substantial societal and economic burdens. Our study and previous research underscore the urgent need for large-scale screening to identify high-risk patients for timely intervention.

Notably, participants who experienced MOF had higher osteoporosis prevalence than those without fractures. Previous studies show most osteoporotic fracture patients have BMD T-scores above -2.5 [6-7], indicating that BMD alone has low sensitivity for fracture prediction. Our results demonstrate FRAX's superiority, with an AUC of 0.683 for predicting MOF compared to 0.662 for femoral neck BMD T-scores alone. This suggests FRAX provides better predictive value than BMD alone for Beijing residents, consistent with Crandall et al.'s 10-year prospective study showing an AUC of 0.698 for FRAX with BMD [13], while acknowledging that FRAX's predictive capacity 仍有改进空间.

Intervention threshold setting based on FRAX follows two main approaches [14].

Fixed thresholds disregard age and sex, such as the U.S. National Osteoporosis Foundation (NOF) guideline recommending treatment when MOF probability 20% or HF probability 3% in osteopenic patients [15], and the Japanese guideline suggesting MOF probability 15% [16]. Age-specific thresholds, such as those from the UK National Osteoporosis Guideline Group (NOGG), set intervention thresholds equal to the fracture probability of women with prior osteoporotic fractures at each age [17]. China's 2017 primary osteoporosis guideline adopted the U.S. NOF thresholds (MOF 20% or HF 3%) [2]. However, Chinese studies demonstrate these thresholds have low sensitivity for predicting fractures [10] or diagnosing osteoporosis [18] in Chinese populations. In our study, only 4 of 49 fracture cases had HF probability >3%, and none exceeded the 20% MOF threshold, yielding sensitivity of just 8.2% (though specificity was 98.6%). Applying these thresholds would miss most fracture patients who could benefit from anti-osteoporosis treatment, highlighting the need for population-specific thresholds.

Our finding that a 2.95% MOF probability maximizes Youden's index (sensitivity 59.2%, specificity 67.6%) provides a reference for establishing appropriate intervention thresholds. However, fracture prevalence varies regionally, necessitating further studies in other Chinese cities and populations. Additionally, threshold determination should incorporate pharmacoeconomic factors including local healthcare resources, cost-effectiveness of anti-osteoporosis medications, and public awareness.

This study has several limitations. First, the relatively small sample size resulted in few fracture events, particularly HF (n=5). Second, participants were not randomly sampled, potentially limiting representativeness of Beijing's general population. Third, the 10-year follow-up rate was modest (46.07%), though baseline comparisons showed no significant differences between followed and lost participants except for age and FRAX probabilities. Fourth, fracture data relied on self-report, introducing recall bias, and vertebral fractures may have been underdiagnosed due to their occult nature, potentially underestimating true fracture incidence. Fifth, lack of periodic assessments during follow-up prevented determination of fracture timing.

Author Contributions

LIU Yangxiaoou was responsible for study implementation, data collation, statistical analysis, figure preparation, and manuscript writing. LIU Yangxiaoou, YU Su, HUANG Kai, YAN Yan, and LI Chao conducted data collection. SUN Yange and DU Xueping developed the primary research objectives. SUN Yange conceived and designed the study, provided quality control, reviewed the manuscript, and takes overall responsibility for the work.

Conflict of Interest

The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.