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ORIGINAL ARTICLE

FRAX® with or without BMD and TBS predicts fragility fractures in community-dwelling rural southern Indian postmenopausal women

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Abstract

Summary This study from southern India showed that FRAX® with or without BMD or TBS predicted fragility vertebral fractures at a cut-off of ≥ 9% for major osteoporotic fracture and ≥ 2.5% for hip fracture with sensitivities of 77–88% and specificities of 55–72%.

Purpose There is limited information available with regard to utility of Fracture Risk Assessment Tool (FRAX® tool) in predicting fragility fractures in Indian postmenopausal women. We studied the performance of 3 categories: FRAX® (without BMD), FRAX® (with BMD), and FRAX® (with BMD and TBS) in predicting fragility vertebral fractures in rural postmenopausal women.

Material and methods It was a cross-sectional study conducted at a south Indian tertiary care center. Rural postmenopausal women ($n = 301$) were recruited by simple random sampling. The risk for major osteoporotic fracture (MOF) and hip fracture (HF) was calculated individually for the 3 categories. The BMD (at lumbar spine and femoral neck) and vertebral fractures were assessed by a DXA (dual energy X-ray absorptiometry) scanner and TBS by TBS iNsight software. ROC curves were constructed, and area under curve (AUC), sensitivity and specificity of FRAX® scores, which would best predict prevalent vertebral fractures (moderate to severe), was computed.

Results The mean (SD) age was 65.6(5.1) years. The prevalence of osteoporosis at spine was 45%, and femoral neck was 32.6%. Moderate to severe vertebral fractures was seen in 29.2% of subjects. The performance of all 3 categories for FRAX® (MOF) and FRAX® (HF) were good (AUC was 0.798, 0.806, and 0.800, respectively, for MOF) at a cut-off score of ≥ 9, and at a cut-off of ≥ 2.5 for HF, it was 0.818, 0.775, and 0.770, respectively. At these cut-offs, sensitivities were 77–89%, and specificities were 55–72% for predicting prevalent vertebral fractures.

Conclusion All three categories of FRAX® showed good performance in predicting fractures in Indian postmenopausal women. Thus, it may be utilized for decision regarding treatment and referral for osteoporosis.

Keywords FRAX® · BMD · Osteoporosis · Trabecular bone score

Introduction

Osteoporosis is the most common metabolic bone disease in postmenopausal women. India has about50 million people living with either osteoporosis or osteopenia, and these figures are expected to rise with an increase in life expectancy [1]. Studies have shown that the prevalence of osteoporosis in India among postmenopausal women ranges between 25 and 62% [2–4]. Osteoporosis could lead to fragility fractures, and the mortality is as high as 20–24% in the first year following hip fracture in those older than 60 years of age [5]. Hence, we are in need of a suitable fracture prediction tool for predicting fractures early, thereby decreasing the morbidity and mortality associated with osteoporosis.

Currently bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) is the gold standard for diagnosing osteoporosis. However, DXA machines available in India are only 0.26/million against the recommended 10.6/million by the International Osteoporosis Foundation (IOF) [6]. As DXA machines are not easily accessible, there is a need for an easily

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available and ethnicity specific screening tool for fracture prediction.

Fracture risk assessment tool (FRAX®) is the most commonly used fracture prediction tool, which predicts the 10 years probability of major osteoporotic fracture (MOF) and hip fracture based on age, body mass index (BMI), and several risk factors with or without bone mineral density [7]. Though it is a cost-effective and validated fracture prediction tool in many countries, it has its own limitations [8].

Thus, this study was conducted to evaluate the performance of FRAX® with and without BMD in predicting the presence of fragility fractures as assessed by VFA (vertebral fracture assessment) in postmenopausal women recruited from a rural community in southern India and to derive population specific cut-offs for FRAX® in predicting fragility fractures.

Materials and methods

This was a cross-sectional study done from December 2018 to April 2019 to assess the utility of FRAX® (with or without BMD/TBS) in predicting the presence of vertebral fractures in postmenopausal women. The study was approved by the institutional review board of Christian Medical College, Vellore (IRB no. 12363/18).

Sample size estimation

Sample size was calculated on the basis of a previously published study by Bansal et al. that looked at the utility of FRAX® in predicting the presence of major osteoporotic and hip fractures [9]. The mean difference of the FRAX® scores between individuals with and without hip fracture was 1.28. Keeping a power of 80% and alpha error of 5%, the required sample size for this study was estimated to be 270. This was calculated using n-master sample calculation software version 2.0.

Study subjects

The study population was recruited from the rural community (3 villages—Alangayam, Govindapuram, and Kothakottai) from the Tirupattur district in the southern India. Initially demographic details of postmenopausal women in this region were archived from district headquarters. Recruitment was undertaken by simple random sampling. The houses in the recruitment area were numbered, and computer generated numbers were utilized for random sampling of the selected houses. Inclusion criteria comprised of postmenopausal women who were ≥ 60 years of age and ambulating independently. Women with a prior diagnosis of osteoporosis, stroke, malignancy, and other conditions leading to immobilization, those on bisphosphonates and bone anabolic agents were excluded. Subjects with past history of spine trauma or surgery and those on indigenous medications without detailed information were also excluded. Among the selected houses, women who met the inclusion and exclusion criteria were recruited after obtaining a written informed consent. There was homogeneity in the ethnicity and cultural practices of the study population in this region. The study flow diagram is shown in Fig. 1.

Data collection

The FRAX® risk factors (history of fragility fractures, parental history of hip fracture, glucocorticoid use, smoking, alcohol use, rheumatoid arthritis, secondary osteoporosis) were assessed and the 10 years risk of major osteoporotic fracture

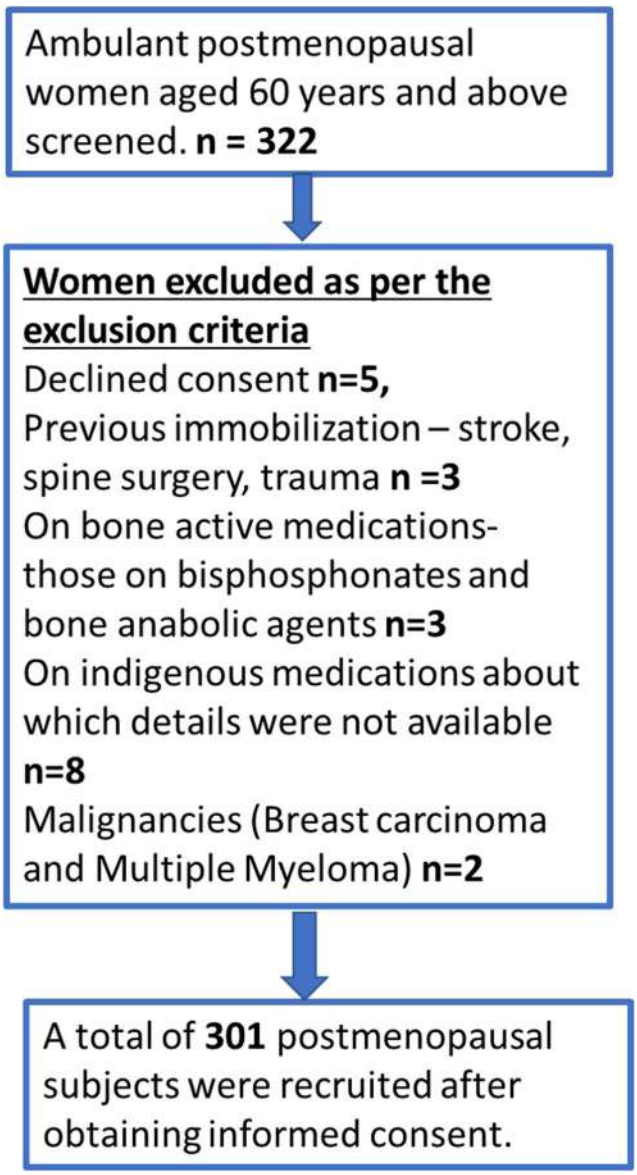

Fig. 1 Flow diagram showing recruitment of study subjects

Table 1 Baseline characteristics of study subjects

Parameter	No vertebral fracture Mean ± SD N = 213	Vertebral fracture Mean ± SD N = 88	p value
Age (years)	64.4 ± 4.1	68.4 ± 5.6	< 0.001
BMI (kg/m^2)	25.7 ± 4.3	25.3 ± 4.7	0.414
Femur neck BMD (g/cm^2)	0.642 ± 0.106	0.571 ± 0.105	< 0.001
Lumbar spine BMD (g/cm^2)	0.832 ± 0.144	0.765 ± 0.152	< 0.001
Mean TBS	1.22 ± 0.09	1.18 ± 0.11	0.01
FRAX MOF (%)	7.6 ± 3.6	14.5 ± 5.9	< 0.001
FRAX HF (%)	2.4 ± 1.9	5.7 ± 3.4	< 0.001

(MOF) and hip fracture (HF) using FRAX® in three categories (FRAX® without BMD, FRAX® with BMD, and FRAX® with BMD and TBS (trabecular bone score)) were calculated. FRAX® assessment was done by one medical professional (first author of this study).The first author received training by reviewing the articles and study materials on FRAX® tool and also by attending a CME program conducted by the national body Indian Society of Bone and Mineral Research (ISBMR), prior to the initiation of the study. In addition, further information on FRAX® tool was also obtained from the online site of IOF (International Osteoporosis Foundation).

BMD at the lumbar spine (L1-L4) and neck of femur (NOF) were measured using a Hologic Discovery A-QDR 4500 DXA (dual-energy X-ray absorptiometry) scanner by the same DXA technician who has an experience of more than 15 years in performing DXA scans at our site. NHANES database was used to calculate T-scores. Vertebral fractures (VF) were quantified using VFA and were classified into mild, moderate, and severe from DXA images using Genant semiquantitative method [10]. A single bone radiologist read the VFA and was blinded to patient information. The moderate and severe category of fractures was only taken to describe the category of VF (presence or absence of fractures). The coefficient of variation (CV) for measurement of BMD at lumbar spine and femoral neck are 1–2% and 2–3%, respectively. The CV for assessment for moderate to severe VF was 3% and 6% for mild fractures.

TBS is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect index of trabecular microarchitecture [11, 12]. TBS (L1–L4) measurements were performed using TBS iNsight software version 3 (Med-Imaps, Bordeaux, France).

Statistical analysis

Data analysis was done using SPSS 17.0 version. Descriptive statistics such as age, BMI, and FRAX® score were reported using mean ± SD. Categorical variables such as FRAX® risk factors were reported using frequency and percentage. The sensitivity, the specificity, and the area under the receiver-operating characteristic (ROC) curve for predicting the presence of vertebral fractures were calculated. The risk for MOF and HF were plotted as a continuous variable against a binomial variable—presence or absence of a moderate/severe vertebral fracture as determined by VFA.

Results

A total of 301 postmenopausal women were recruited in this study. The mean (SD) age of the subjects was 65.6(5.1) years and the mean (SD) BMI was 25.6(4.4) kg/m^2. When baseline characteristics were compared, it was found that those with vertebral fractures were older and had lower BMD, TBS, and

Table 2 Prevalence of FRAX risk factors in study subjects

Parameter	Total N = 301 (%)	No vertebral fractures N = 213 (%)	Vertebral fractures N = 88 (%)	p value
Previous fragility fracture	30 (10)	8 (3.8)	22 (25)	< 0.001
Parental hip fracture	18 (6)	6 (2.8)	12 (13.6)	0.001
Smoking	1 (0.3)	0	1 (1.1)	0.292
Alcohol	1 (0.3)	0	1 (1.1)	0.292
Glucocorticoids	17 (5.6)	3 (1.4)	14 (15.9)	< 0.001
Rheumatoid arthritis	8 (2.7)	0	8 (9.1)	< 0.001
Secondary osteoporosis	20 (6.6)	4 (1.9)	16 (18.2)	< 0.001

Table 3 FRAX in three categories predicting vertebral fractures

Parameter	Sensitivity	Specificity	AUC	95% CI	p value
Prediction of prevalent vertebral fractures with FRAX/MOF cut-off of ≥ 9%					
FRAX − BMD	87%	72%	0.840	0.785–0.894	< 0.001
FRAX + BMD	85%	72%	0.837	0.785–0.889	< 0.001
FRAX + BMD + TBS	88%	55%	0.831	0.777–0.885	< 0.001
Prediction of prevalent vertebral fractures with FRAX/HF cut-off of ≥ 2.5%					
FRAX − BMD	88%	67%	0.818	0.762–0.873	< 0.001
FRAX + BMD	77%	68%	0.775	0.718–0.832	< 0.001
FRAX + BMD + TBS	81%	59%	0.770	0.711–0.829	< 0.001

higher risk of MOF and HF compared with those without vertebral fractures (assessed by VFA) (Table 1).

FRAX® risk factors were significantly higher among those with vertebral fractures compared with those without vertebral fractures (Table 2). Eighty eight (29.2%) subjects had either moderate or severe vertebral fractures, assessed by VFA. One hundred and fifty (49.8%) subjects had osteoporosis at either lumbar spine or NOF (135/301 (44.9%) at LS and 98/301 (32.6%) at NOF).

Performance of FRAX®/MOF to predict the presence of vertebral fracture

When ROC was plotted (Fig. 1) to find how FRAX®/MOF predicted the presence of vertebral fractures, FRAX® in all three categories predicted the presence of vertebral fractures with a good area under the curve of > 0.8 (Table 3).When different cut-offs for FRAX® without BMD were evaluated, it was found that a FRAX/MOF cut-off of ≥ 9% predicted the presence of vertebral fractures with a sensitivity of around 87% and specificity of 72% (Table 4).

Table 4 FRAX without BMD (FRAX − BMD) predicting prevalent vertebral fractures

FRAX − BMD	Sensitivity	Specificity	Youden index
Different cut-offs of FRAX/MOF for predicting vertebral fractures			
6%	90%	40%	0.3
9%	87%	72%	0.6
10%	76%	80%	0.56
13.5%	53%	93%	0.46
Different cut-offs of FRAX/HF for predicting vertebral fractures			
1.5%	91%	46%	0.37
2%	90%	57%	0.47
2.5%	88%	67%	0.55
3%	80%	73%	0.43

Performance of FRAX®/HF to predict the presence of vertebral fracture

Similarly, FRAX® in all three categories predicted prevalent vertebral fractures (Fig. 2 a) with a good area under the curve of 0.77–0.8 (Table 3).Among the different cut-offs for FRAX® without BMD, it was found that a cut-off of ≥ 2.5% for HF predicted vertebral fractures with a sensitivity of around 88% and specificity of 67% (Table 4).

Utility of FRAX to predict the presence of vertebral fractures

Taking a FRAX®-MOF, cut-off of ≥ 9%, 77/88 patients (87%) were detected to have vertebral fractures. With a FRAX®/ HF cut-off of ≥ 2.5%, 78/88 patients (89%) were detected to have vertebral fractures (Table 5).

Discussion

In the present study, the prevalence of osteoporosis was about 50%, and 30% had either moderate or severe vertebral fractures assessed by VFA. A revised cut-off for FRAX®-MOF at ≥ 9% and FRAX®-HF at ≥ 2.5% was detected around 90% of subjects with vertebral fractures.

Currently most guidelines suggest treatment of osteoporosis based on BMD by DXA [13–15]. In addition to BMD, NOGG (National Osteoporosis Guideline Group) and NOF (National Osteoporosis Foundation) have incorporated FRAX® in their guidelines for treatment decisions [13, 14]. In resource poor settings like India, FRAX® serves as an ideal fracture prediction tool [8]. However, the utility of this tool needs to be tested in our population, and intervention thresholds specific to our population need to be derived.

The gender- and age-specific fragility fracture incidence may differ from country to country [16]. In addition, risk

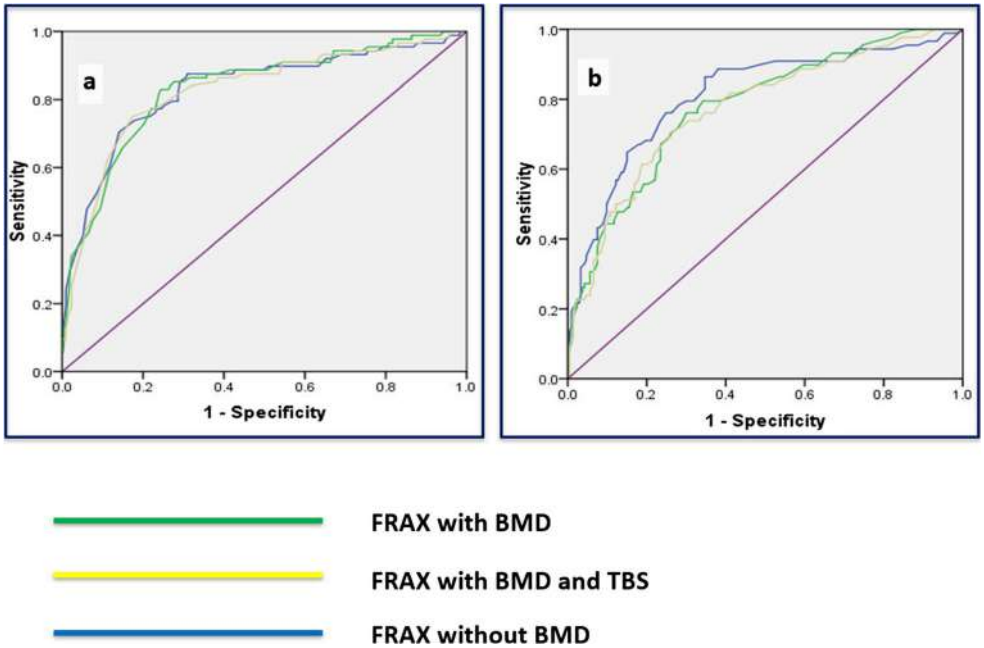

Fig. 2 **a** Shows the ROC plot for assessing FRAX for major osteoporotic fracture without BMD (blue color); FRAX with BMD (green color); and FRAX with BMD and TBS (yellow color) against the presence or absence of vertebral fracture. **b** Shows the ROC plot for assessing FRAX for hip fracture without BMD (blue color); FRAX with BMD (green color); and FRAX with BMD and TBS(yellow color) against the presence or absence of vertebral fracture

factors of fragility fracture may also have geographical variations. FRAX® needs to be validated for each country based on their own epidemiology of fractures and associated mortality [8]. The NOF set a 3% probability of hip fracture and a 20% 10-year probability of a major fracture as thresholds for treatment in women with osteopenia based on health economic analysis that looked at cost-effectiveness of therapeutic intervention [14]. Although this has been adopted by many countries as an intervention threshold, this may not be the best approach. Recently, FRAX® has been utilized to estimate fracture risk in a hospital-based population from northern India [9]. However, it need to be noted that FRAX® India is based on the fragility fracture incidence data from Singapore Indians as robust data from India is not yet available [17]. Hence, there is a need for large population studies from India to study the epidemiology of fractures in our country in order to calculate the 10 years absolute fracture risk.

The National Osteoporosis Guideline Group (NOGG) has developed an age dependent cut-off to be used as the intervention threshold in postmenopausal women and elderly men [18]. This is based on the concept that women without fracture merit treatment if their risk of fracture is similar to or exceeds that of an average woman with a prior fracture. Thus it attempts to embrace fairness and equity of access to treatment.

A systematic review by NOGG in 2016 suggested that the intervention threshold should be country specific as the epidemiology of fractures is different in each country [19]. The present study has derived a cut-off specific to our population, which predicted vertebral fractures in around 90% of our subjects.

In a study from northern India, Bansal et al. found that FRAX®-MOF and FRAX®-HF were significantly higher in individuals with fragility fractures compared with those admitted without fragility fractures (FRAX®-MOF, 7.34 ± 4.41 versus 5.64 ± 4.3; $p = 0.001$; FRAX®-HF2.95 ± 3.13 versus 1.67 ± 2.21; $p < 0.001$). The area under the curves was 0.627 for FRAX®-MOF and 0.654 for FRAX®-HF. For FRAX®-MOF, a cut-off of 2 has 90% sensitivity but only 15% specificity; FRAX®-HF, at a cut-off of 0.3, had about 90% sensitivity and 20% specificity [9]. However, the present study recruited subjects from the community and is probably a better representative of the general population. Similar studies from other ethnicities have suggested different thresholds for FRAX® in their countries. In a Polish study by Badurski

Table 5 FRAX with revised cut-offs predicting vertebral fractures

FRAX cut-off		Vertebral fractures n (%) N = 88	No vertebral fractures n (%) N = 213
Major osteoporotic fracture	High risk (≥ 9%)	77/88 (87)	60/213 (28)
	Low risk (< 9%)	11/88 (13)	153/213 (72)
Hip fracture	High risk (≥ 2.5%)	78/88 (89)	75/213 (35)
	Low risk (< 2.5%)	10/88 (11)	138/213 (65)

et al., FRAX with or without BMD predicted risk of MOF and HF in a similar manner. The intervention threshold in this study was set as 18% for MOF and 9% for HF [20]. In a study from Hong Kong, the optimal cut-off point for the 10-year probability of a major fracture was 9.95% [21]. This prospective study was part of Hong Kong Osteoporosis study on 2266 Chinese postmenopausal women for a period of 4.5 years, which looked at the development of incident fragility fractures. In a study by Zhang et al. in the Chinese population, thresholds for a 10-year probability of major osteoporotic fracture and hip fracture were calculated with BMD, and the cut-offs proposed were 4.0 and 1.3%, respectively [22]. In a Swiss-based study comprising of individuals ≥ 50 years of age, cost-effective FRAX-based intervention thresholds and cost effectiveness of treatment with alendronate were estimated. In Swiss women and men aged ≥ 50 years, treatment aimed at decreasing fracture risk was cost-effective with a 10-year probability for a major osteoporotic fracture at or above 13.8% (range 10.8% to 15.0%) and 15.1% (range 9.9% to 19.9%), respectively. Based on this study, a FRAX threshold of 15% was proposed for prediction of a major osteoporotic fracture in Swiss men and women [23].

The present study is the first community-based study from India to evaluate the utility of FRAX® in predicting fragility vertebral fractures. It also derived a specific cut-off that predicted vertebral fragility fractures in our postmenopausal women.

However, the present study is limited by its cross-sectional design and only looked at prevalent vertebral fractures as a dichotomized variable. Further, as this study was done in postmenopausal women from rural southern India, validation of these findings is warranted in a cohort separate from ours.

In conclusion, FRAX® may be used as a cost-effective screening tool in Indian setting. A FRAX®-MOF cut-off of ≥ 9% and FRAX®-HF cut-off of ≥ 2.5% predicted the presence of vertebral fractures with good sensitivity and reasonable specificity. Nevertheless, further prospective studies are needed to substantiate these findings.

Compliance with ethical standards

Conflict of interest None.

Ethical approval The study was approved by the institutional review board of Christian Medical College, Vellore (IRB no. 12363/18).

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