Original article

Ability of FRAX Sri Lanka adjusted for trabecular bone score to discriminate between postmenopausal women with a recent fracture and without a fracture

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ABSTRACT

Objectives: We evaluated the ability of fracture risk assessment tool (FRAX) Sri Lanka to discriminate between women with a recent fracture and without a fracture, when trabecular bone score (TBS) is added to the calculation.
Methods: We studied 394 women without previous fractures and 87 women who underwent dual energy X-ray absorptiometry within 3 months after the first fragility fracture. Fracture probabilities (FP) were estimated with and without TBS using Sri Lankan FRAX model and their ability to discriminate those with and without fracture was tested.
Results: Women without fractures had higher bone mineral densities (BMDs) and lower FPs, compared to those with a recent fracture. Area under curves of receiver operating characteristic for FPs unadjusted were not different from those adjusted for TBS. The odd ratios of FPs unadjusted were not different from those of adjusted. The FPs estimated with TBS were higher, hence the intervention thresholds (ITs) were higher compared to FPs estimated without TBS. Thirty-two percent of women without previous fracture were above the ITs and the inclusion of TBS increased this to 36%. The integrated discriminatory index analysis showed a 8% increase in the discriminatory slope.
Conclusions: The inclusion of TBS to Sri Lankan FRAX did not show an added advantage in discriminating between postmenopausal women with a recent fracture and without a fracture. TBS inclusion in fracture risk calculation among those without previous fractures, however, showed a marginal increase in the number of women above ITs.

1. Introduction

Therapeutic decisions in osteoporosis are now made based on fracture risk estimations than mere BMD values [1,2]. The FRAX is widely used for the estimation of fracture risk and available in many countries. In 2016, FRAX was available in 63 countries covering 79% of the world population [2]. It has been validated in numerous ways and has been included in the risk estimation in clinical trials [3].

Several modifications have been introduced to improve the accuracy of FRAX-based risk estimations. These include adjusting FRAX output for the discrepancy of T-scores between spine and femoral neck [4] and for varying glucocorticoid doses [5]. Adjusting FRAX output for Trabecular Bone Score (TBS) was introduced later to account for the microarchitectural deterioration of the bone tissue which is not directly captured in the conventional FRAX input variables. TBS is a gray-level texture measurement on lumber spine DXA images reflecting information relating to trabecular microarchitecture. FRAX adjusted for TBS perform better than

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unadjusted FRAX in predicting incident fracture and discriminating prevalent fractures, independent of BMD and other clinical risk factors [6—8]. The license of TBS software is relatively expensive and not widely available. Its availability is restricted to a very limited number of centers in South Asia and this is evident by the lack of studies on TBS in this region.

The prevalence of osteoporosis and the incidence of fragility fractures have a considerable geographical variation. Accordingly, FRAX algorithms are country-specific and for a given set of clinical risk factors the fracture probabilities estimated by different FRAX models show a wide variation [9]. It is unclear whether adjusting FRAX for TBS generates the same results across all FRAX models as some studies have failed to find an added advantage of TBS adjustment [10]. This study was done to determine whether adjusting the Sri Lankan FRAX model for TBS would improve its ability to discriminate between postmenopausal women with a recent fracture and without a previous fracture. We used 2 groups of postmenopausal women, one without a previous fracture and other with a recent fracture.

2. Methods

The study sample consisted of consecutive 521 postmenopausal women who underwent DXA for the evaluation of fracture risk in our tertiary care referral center. This state-owned tertiary care center provides DXA facility, free of charge, for the entire Southern province of the country. The study subjects belonged to all socio-economic strata and all ethnicities, and were postmenopausal.

All women had BMD measurements of the lumber spine (L1-L4), femoral neck, and total hip with a central DXA scanner (Discovery, Hologic Inc., Marlborough, MA, USA), and estimation of TBS with TBS iNsight software-version 3 (Medimaps, Switzerland). All scans were done adhering to the manufacturers' protocols and the *in-vitro* precision of the scanner was ensured on each scanning day. Height and weight were measured with a stadiometer, and clinical risk factors including those captured in FRAX risk calculation were recorded using a predesigned questionnaire.

The study sample included 87 women who had suffered a fragility fracture within a 3-month period before undergoing DXA. These included 60 radiographically confirmed vertebral fractures and 27 distal forearm fractures. None of these women has had hip fractures, previous fractures or prolonged immobilization. In order to get a fracture free group of women for comparison, we excluded women who had fractures more than 3 months before DXA evaluation (n = 40). Clinical notes including clinic follow up data, referral forms, and previous radiographs were perused for this information.

We estimated major osteoporotic fracture probability (MOFP) and hip fracture probability (HFP) using the Sri Lankan FRAX model based on clinical risk factors and femoral neck BMD. These risk scores were recalculated after the inclusion of TBS. The study was approved by the Ethics review committee of the Faculty of Medicine, Galle (Ref no 09.03.2016:3.3) and all patients filled an informed consent form before data collection. All procedures performed were in accordance with the ethical standards of the Ethics review committee of the Faculty of Medicine, Galle and the 1964 Helsinki declaration and its later amendments.

BMDs, TBS and fracture probabilities (unadjusted and TBS adjusted), were compared between women with a recent fracture and without a fracture. Independent-t test was used to compare age, BMDs and TBS (described as mean and SD) which were normally distributed and the Mann-Whitney U test was used for fracture probabilities which were skewed (described as median and interquartile range). The area under curve (AUC) for each fracture probability was estimated by ROC analysis considering fracture outcome as the state variable and fracture probability as the independent variable. The best cut point (intervention threshold) was determined based on either the point closest-to- the (0,1) corner of the ROC plane or the point maximizing the Youden index. The Youden index is used to determine the most appropriate cut point in ROC analysis as it captures both sensitivity and specificity of a dichotomous test [11]. Odds ratio for each fracture probability was also determined with binary logistic regression with fracture outcome as the dependent variable and fracture probability as the independent variable. The proportion of women above intervention thresholds were estimated with and without TBS among women without previous fractures, and integrated discriminatory index was calculated to detect the effect of inclusion of TBS among them. Statistical significance was set at P < 0.05 in all analyses.

3. Results

The study sample comprised of a group of postmenopausal women (n = 521) aged between 40 and 84 years of age. Forty women were excluded since they had fractures more than 3 months before the scanning date. Of the remaining 394, 12 were current glucocorticoid users (any dose) while 4 gave history of chronic inflammatory arthritis. None of them were current smokers or alcohol users. Eighty-seven of them had a previous fragility fracture suffered within 3 months of the DXA scan (radiographically confirmed vertebral fractures 60 and distal forearm fractures 27).

Compared to women with fractures, women without fractures had significantly higher regional BMDs and lower fracture probabilities, both major osteoporotic and hip, unadjusted and adjusted for TBS (Table 1). TBS showed significant correlations with age (r = 0.46), spine BMD (r = 0.55), femoral neck BMD (r = 0.43), unadjusted MOFP (r = −0.50), unadjusted HFP (r = −0.45), MOFP adjusted for TBS (r = −0.57), and HFP adjusted for TBS (r = −0.50) (P < 0.01 for all).

All fracture probabilities, unadjusted and adjusted, had high AUCs indicating their ability to discriminate women with and without fractures. This observation was concordant with the odds ratios seen after binary logistic regression analysis. Adjusting fracture probabilities for TBS, however, did not change the AUCs (Fig. 1) and odds ratios materially.

The intervention threshold of MOFP changed from 9% to 11% following TBS adjustment. However, the change of HFP after TBS adjustment was only marginal (3.2%–2.7%) (Table 2). When women without previous fractures were analyzed without inclusion of TBS, 32% were above the intervention thresholds. This proportion increased to 36% when TBS was included in the calculation of fracture thresholds. In the integrated discriminatory index analysis, the discriminatory slope was 8% higher when TBS was included in the calculations.

4. Discussion

Our data suggest that adjusting FRAX output for TBS does not improve its ability to discriminate patients with a recent fracture and without a prevalent fracture. The AUCs of MOFP and HFP, adjusted for TBS were similar to those of unadjusted probabilities, and odds ratios were broadly similar. The correlations seen between TBS and adjusted fracture probabilities were only modest (r = 0.5) and TBS would account for only 25% (R^2) variation of adjusted fracture probabilities. Women with a recent fracture had lower BMD, TBS, and higher fracture probabilities compared to women without a fracture. Adjusted fracture probabilities were relatively higher than unadjusted values hence the intervention thresholds of FRAX plus TBS were higher. Although the change of HFP was marginal (2.7%–3.2%), the 2% difference seen in the MOFP

Table 1
Descriptive data of the 481 postmenopausal women included in the study.

Variable	Entire sample (n = 481)	Women without fracture (n = 394)	Women with fracture (n = 87)
Mean (SD)			
Age, yr	63.1 (10.4)	62.6 (10.4)	69.0 (7.8)
Spine BMD, g/cm^2	0.718 (0.156)	0.726 (0.157)	0.617 (0.114)
FN BMD, g/cm^2	0.690 (0.158)	0.698 (0.157)	0.594 (0.132)
TBS	1.15 (0.09)	1.19 (0.10)	1.11 (0.08)
Median (IQR)			
MOFP unadjusted for TBS, %	5.5 (2.8—9.4)	5.2 (2.6—8.6)	15.0 (12.0—21.0)
HFP unadjusted for TBS, %	1.4 (0.3—3.4)	1.1 (0.3—3.0)	6.5 (3.1—10.5)
MOFP adjusted for TBS, %	7.3 (3.6—12.0)	6.7 (3.4—10.8)	18.1 (14.7—24.0)
HFP adjusted for TBS, %	1.9 (0.5—4.4)	1.6 (0.5—3.8)	7.1 (3.5—11.7)

P < 0.001 for all comparisons between women with and without fracture.
SD, standard deviation; BMD, bone mineral density; FN, femur neck; TBS, trabecular bone score; IQR, interquartile range; MOFP, major osteoporotic fracture probability; HFR, hip fracture probability.
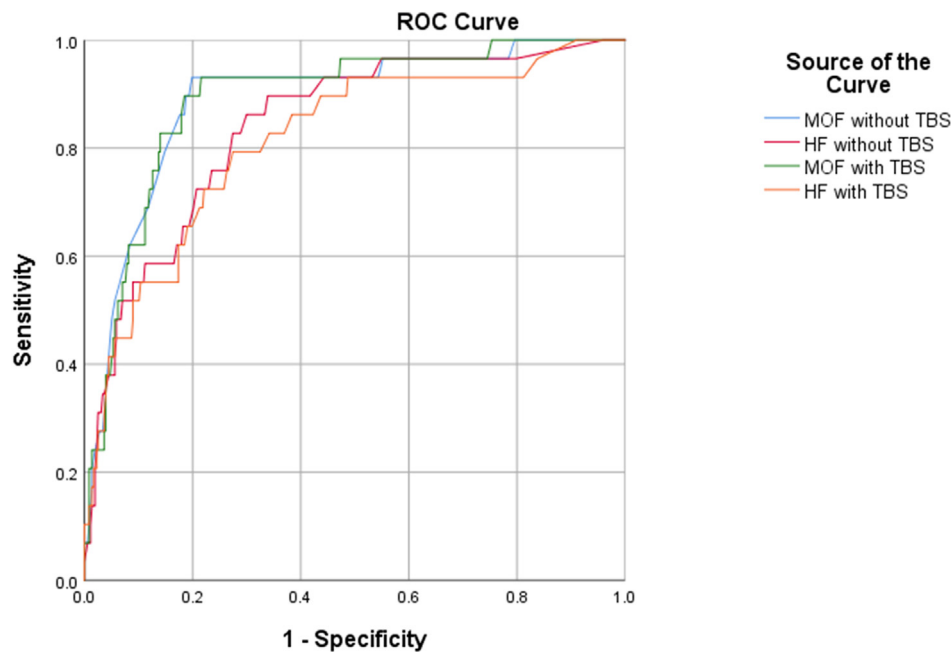

Fig. 1. Receiver operating characteristic (ROC) curves for major osteoporosis fracture (MOF) and hip fracture (HF) probabilities, TBS adjusted and not adjusted.

Table 2
AUCs of ROC analyses, intervention thresholds and odds ratios of fracture probabilities.

Variable	AUC (SE)	Intervention threshold	Odds ratio (95% CI)
MOFP unadjusted	0.89 (0.03)*	9.0%	1.22 (1.15—1.29)
HFP unadjusted	0.84 (0.04)*	2.7%	1.26 (1.16—1.39)
MOFP adjusted for TBS	0.89 (0.03)*	11.0%	1.19 (1.13—1.26)
HFP adjusted for TBS	0.81 (0.04)*	3.2%	1.22 (1.14—1.31)

*P = 0.001.
AUC, area under curve; ROC, receiver operating characteristic; SE, standard error; MOFP, major osteoporotic fracture probability; HFR, hip fracture probability; TBS, trabecular bone score.

needs attention. The inclusion of TBS in the fracture risk calculation of postmenopausal women without previous fractures, however, showed a modest (5%) increase in the proportion of those above the intervention thresholds.

The TBS captures trabecular bone microarchitecture based on grey-level texture measurement on total spine DXA images and is an independent risk predictor of fragility fractures. TBS predicts both incident and prevalent fractures regardless of BMD or FRAX based fracture probabilities [7,8,12]. Many studies have shown that TBS adjusted for fracture probabilities predict fractures better than TBS unadjusted fracture probabilities [13,14]. Apart from postmenopausal women, this added value of TBS has been demonstrated also among HIV-positive patients [15], and clinical subpopulations such as diabetes [16], and thalassemia [17].

The added value of TBS, however, is not consistently proven and our observations are consistent with the studies that have not shown this incremental benefit. In a meta-analysis (2016), the FRAX plus TBS resulted in only a small increase in the gradient of risk of

fracture (1.76 vs 1.70), and the change in the gradient of risk of hip fractures was only marginal (2.25 vs 2.22). The authors, although they supported the use of TBS adjustment, recommended that the impact of the adjustment needs further exploration [14]. Jain and Vokes showed a variation of TBS performance based on the ethnicity of US women [18]. The association of TBS and prior fracture was stronger among Caucasian Americans compared to African and Mexican Americans [18]. No improvement was observed in FRAX fracture predictability by adding TBS in older Japanese women [10]. Furthermore, AUCs of FRAX without and with TBS were not different among Japanese men studied by Iki et al [19]. In a similar study Lee et al found that addition of TBS did not improve the fracture predictability of FRAX output in women with osteoporosis [20].

Reasons for the inability of the TBS to improve FRAX output in certain studies are unclear. This could partly be due to the differences in study methods and study samples. Among Japanese, Tamaki et al found an added value of FRAX plus TBS [21], while Su et al [10] failed to find such an advantage. Data are insufficient to conclude that TBS has a limited role in Asian populations. TBS facilities are relatively expensive and the availability is restricted to few centers in South Asian countries. More studies are needed to ascertain the advantage of TBS among Asian postmenopausal women.

The intervention thresholds we observed are consistent with the revised Sri Lankan intervention thresholds published recently [22]. The revised intervention thresholds for MOFP and HFP published in 2019 based on the Sri Lankan FRAX were 9% and 3%, respectively, and similar to the 9% and 2.7% observed in this analysis. The intervention thresholds based on FRAX plus TBS, however, were somewhat higher (MOFP 11% vs 9%, and HFP 3.2% vs 2.7%). Although the HFP intervention threshold of 3% can be considered acceptable for both FRAX adjusted and unadjusted after rounding-off the 2 values, MORP intervention threshold of 11% should be taken into consideration when deciding on interventions based on FRAX plus TBS outputs. On FRAX output without TBS included. Using MOFP intervention threshold of 9% and HFP intervention threshold of 3%, 128 women of the study sample of 394 (32%) were found to be above the thresholds. On FRAX plus TBS, using MOFP intervention threshold of 11% and HFP intervention threshold of 3%, 153 women (36%) were above the thresholds and this difference was not statistically significant (P = 0.063). Similar observations has been made by Su et al where TBS-adjusted FRAX reclassified only 5% of men on major osteoporotic fracture prediction [10].

The current study has a few limitations. The number of women with fractures included in the study was small and this may have limited the accuracy of estimations. Further, these patients have had fractures within 3 months of undergoing DXA scanning, and immobility following fractures could have altered their BMD. We have included a few patients who had natural menopause between 40 and 50 years of age. Apart from premature menopause, these patients were free of bone active diseases and medications and they were unlikely to influence the results.

5. Conclusions

We were unable to find an added advantage of FRAX-plus TBS compared to FRAX in discriminating postmenopausal women with a recent fracture and without a fracture. Our data are concordant with other studies which also failed to find improved performance of FRAX plus TBS in this regard. When the majority of studies have shown an added advantage of including TBS in fracture risk calculation, the reasons for not observing such an advantage among our study subjects need further exploration.

Conflicts of interest

CRediT author statement

Acknowledgments

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