

Association between trabecular bone score, 10-year probability risk for fracture, and vertebral fractures in rheumatoid arthritis

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ABSTRACT

Objectives: The aim was to assess the association and predictive value of trabecular bone score (TBS), fracture risk assessment tool (FRAX), and TBS-adjusted FRAX with prevalent vertebral fractures (VFs) in patients with rheumatoid arthritis (RA).

Methods: Patients diagnosed with RA were included in this cross-sectional study. Clinical data and laboratory tests were collected on the same day as the dual-energy x-ray absorptiometry (DXA) scan. TBS, bone mineral density (BMD), and vertebral fracture assessment (VFA) were obtained from the DXA scan. We used the FRAX tool to assess the 10-year probability of major osteoporotic fracture (MOF-FRAX) and hip fracture (HF-FRAX) with and without BMD. These parameters were further adjusted for TBS. Patients with prevalent VFs were defined as those with moderate to severe VFs from T4 to L4. VFs presence was used as the binary variable in the logistic regressions and receiving operator characteristics (ROC) curves analysis.

Results: Sixty-nine patients were enrolled, with 55.1 % being postmenopausal. The mean TBS was 1.328 ± 0.104 . Osteoporosis according to the WHO criteria was present in 39 patients (56.5 %), and six patients (8.7 %) had VFs with thoracic predominance (66.67 %). Univariate and multivariate logistic regression analyses did not show an association between TBS and vertebral fractures, but FRAX scores indicated such an association. The area under the curve (AUC) with 95 % confidence intervals (CI) for the MOF-FRAX score with BMD, MOF-FRAX score without BMD, TBS-adjusted MOF-FRAX score, and TBS were 0.837 [0.686–0.988], 0.795 [0.629–0.961], 0.778 [0.571–0.984], and 0.515 [0.298–0.731], respectively.

Conclusion: In our RA patients, FRAX scores were associated with vertebral fractures (VFs), while TBS was not. The MOF-FRAX score combined with BMD, showed the best AUC for VFs in this population.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic and joint disease that is highly prevalent, particularly among elderly females (Guo et al., 2018). Patients with RA are at increased risk for osteoporosis and fractures due to disease-related factors and glucocorticoid (GC) use (Staa et al., 2006; Angeli et al., 2006; Leufkens and Cooper, 2002). Osteoporosis is a silent disease with enormous health and economic impacts from fragility fractures (Burge et al., 2007). This comorbidity severely affects the quality of life of RA patients (Varacallo and Fox, 2014).

Currently, bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is the most widely used parameter for diagnosing osteoporosis. A T-score is the number of standard deviations between a patient's mean BMD and the population mean for a sex- and

race-matched reference group, and helps to compare the patient's bone density with the average of the reference population (Krug and Langaker, 2024). The World Health Organization (WHO) (Kanis and Kanis, 1994) defines T-scores as: ≥ -1.0 : normal, -1.0 to -2.5 : osteopenia, ≤ -2.5 : osteoporosis, and ≤ -2.5 with fragility fracture: severe osteoporosis. If left untreated, osteoporosis can lead to a damaging cycle of recurrent fractures, often resulting in disability and premature death. In appropriate patients, effective anti-fracture medications can prevent fractures and improve health outcomes. The benefits of early diagnosis and treatment are well documented, as treatment reduces the incidence of fractures, thereby preventing injury, disability, and excess mortality (LeBoff et al., 2022). However, fractures can occur in patients who are not considered at risk based on BMD (Schuit et al., 2004; Pasco et al., 2006). In addition, RA is common in the elderly population, who usually

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have associated degenerative disease, affecting the spine and the joints, leading to BMD overestimation (Masud et al., 1993; Liu et al., 1997).

Efforts are therefore being made to develop non-invasive and practical tools that will hopefully help to accurately assess bone fragility risk on an individual basis. Hence, the fracture risk assessment tool (FRAX) was developed to evaluate the 10-year probability of bone fragility fractures in females and males over the age of 40. This tool relies on selected clinical risk factors for fracture, including RA. Adjusted versions of FRAX, established according to the local epidemiological data, are available for most countries (Chapurlat, 2013). In addition, the trabecular bone score (TBS) is derived from texture analysis of 2D DXA images of the lumbar spine by measuring the local mean variation of pixel gray levels (Pothuaud et al., 2009). This easy-to-use tool has been correlated with bone microarchitecture and macro-architecture, providing information independent of BMD (the Scientific Committee of the GRIQ (Groupe de Recherche et d'Information sur les Ostéoporoses) et al., 2012; Roux et al., 2013; Pothuaud et al., 2008). TBS has shown added value in fracture discrimination, particularly in postmenopausal women, with a large body of literature. Secondary osteoporosis is a very challenging situation where TBS has shown some puzzling results (Kim et al., 2016; Bréban et al., 2012). The study of bone in RA patients is very complicated, as a myriad of complex factors may contribute to bone loss, with potentially different effects on the current bone diagnostic tools. Therefore, in the present study, we aimed to evaluate the association between TBS, FRAX, TBS-adjusted FRAX, and prevalent vertebral fractures in our RA patients free of bone-damaging comorbidities. Second, we evaluated the discriminative value of each bone parameter in predicting vertebral fractures.

2. Materials and methods

2.1. Study population

This cross-sectional study included patients with RA who fulfilled the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2010 criteria (Aletaha et al., 2010). They were recruited in our rheumatology department between December 2021 and January 2022. Patients aged between 40 and 90 years were included in the study. Initial exclusions based on patient history included known diabetes, thyroid disease, hyperparathyroidism, cancer, cirrhosis, and chronic kidney disease. Secondary exclusions were based on renal clearance <70 mL/min and glycated haemoglobin >6.5 % (these laboratory tests were performed at the time of current enrolment). Patients who were currently taking osteoporosis medication or had a body mass index (BMI) >36 kg/m² were also excluded. The study was conducted per the declaration of Helsinki, and all patients provided informed written consent prior to the study.

2.2. Clinical data

Clinical assessment included demographic data: age, height and weight on the same scale, and calculation of BMI by dividing weight by height squared (kg/m²). Disease duration was the elapsed time between the onset of the first disease-related symptoms and enrollment. In addition, history of all low trauma fractures (site, date, number of fractures, parental hip fracture), smoking, and alcohol consumption were collected using a questionnaire filled in by the physician and patients' data report. Age and duration of menopause were recorded, and postmenopausal women were defined as those who had not had a period for one year. The use of oral GCs (current daily dose, duration in months, cumulative dose of prednisone equivalent), disease-modifying anti-rheumatic drugs (DMARDs), and biological agents were also detailed. RA activity was assessed by the tender joint count, swollen joint count, C-reactive protein (CRP) level, and the Disease Activity Score for 28 joints (DAS28) (Aletaha et al., 2005) while the severity was quantified by the Health Assessment Questionnaire (HAQ) score (Guillemin et al.,

1991).

2.3. Bone parameters

Bone mineral density of the lumbar spine, hip, and 1/3 of the non-dominant forearm was assessed by the same DXA device (Horizon, QDR®, APEX software, Hologic, Bedford, MA, USA). Lumbar spine BMD was calculated for the first to fourth vertebrae and given in g/cm². We excluded vertebrae with fractures or degenerative changes causing BMD more than one standard deviation (SD) greater or lower compared with the immediately adjacent vertebrae, following the International Society for Clinical Densitometry rules (ISCD) (Lewiecki et al., 2004). Osteopenia was defined as a T-score below -1.0, and osteoporosis at or below -2.5 at any site according to the WHO classification (Kanis and Kanis, 1994).

Lumbar spine TBS was calculated at the same regions of interest used for BMD measurements using TBS iNsight software (version 3.0.2.0, Med-Imaps, Pessac, France). Subjects were divided into two groups according to their TBS values: low ≤1.310 and normal TBS > 1.310, based on a recent meta-analysis (McCloskey et al., 2016).

We used the FRAX tool to assess the 10-year probability of major osteoporotic fracture (MOF-FRAX) and hip fracture (HF-FRAX). The online tool, adapted to our setting, calculates probabilities based on risk factors alone or with adjustment for femoral neck BMD (MOF-FRAX and HF-FRAX with BMD). Then, we added TBS values and calculated the FRAX probabilities for each patient using both BMD and TBS (MOF-FRAX/TBS and HF-FRAX/TBS). The TBS-adjusted FRAX probabilities for HF and MOF were calculated using the country-specific tool provided on the FRAX website (<https://www.sheffield.ac.uk/FRAX/tool.aspx?country=54>).

2.4. Vertebral fractures assessment

Two readers separately evaluated prevalent VFs from the instant vertebral assessment (IVA) (Greenspan et al., 2001). Vertebral fracture severity was graded visually without direct vertebral measurement as follows: normal (grade 0); mildly deformed (grade 1: approximately 20–25 % reduction in anterior, mid, and/or posterior height); moderately deformed (grade 2: approximately 25–40 % reduction in anterior, mid, and/or posterior height); and severely deformed (grade 3: approximately 40 % or greater reduction in anterior, mid, and/or posterior height). In case of discordance concerning a fracture, a third reader was consulted, and an average estimation was obtained. Patients with moderate to severe VFs in the thoracic and lumbar spine (T4 to L4) according to Genant criteria were defined as patients with prevalent VFs (Genant et al., 2009).

2.5. Statistical analysis

All statistical analyses were performed using SPSS 20.0 (IBM Corp. SPSS Inc., Chicago, IL). For each variable, a descriptive study was conducted. Continuous variables were described using means with their standard deviation or median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Demographic features, clinical characteristics, and parameters associated with fracture were compared using the student *t*-test for normally distributed continuous variables, the Mann-Whitney for asymmetric distribution, and Chi-square test for categorical variables. Univariate logistic regressions were conducted to identify parameters associated with vertebral fractures as the dependent variable. Subsequently, a multiple logistic regression was performed, adjusting for a model based on disease activity (DAS28CRP), HAQ, body mass index, and the duration of glucocorticoid use. Odds ratio (OR) with 95 % confidence interval were given. TBS, BMD, and FRAX scores were evaluated for their ability to detect prevalent VFs by determining the area under the receiving operator characteristics (ROC) curve. Statistical significance was

established at $p < 0.05$.

3. Results

The study included 69 RA patients aged from 40 to 81 years old. **Table 1** summarizes the characteristics of our patients. Their mean TBS was 1.328 ± 0.104 . The study population included 4 (5.8 %), 26 (37.7 %), and 39 (56.5 %) subjects with normal BMD, osteopenia, and osteoporosis, respectively. Six patients (8.7 %) had moderate to severe VFs

Table 1
Characteristics of rheumatoid arthritis (RA) patients with and without vertebral fractures (VFs).

	RA patients (n = 69)	VFs group (n = 6)	Non-VFs group (n = 63)	p value
	Mean \pm SD / n (%) / Median (IQR)			
Age (year)	56.23 \pm 10.04	63.17 \pm 11.72	55.57 \pm 9.72	0.08
BMI (Kg/m ²)	26.98 \pm 4.84	27.82 \pm 3.02	26.91 \pm 4.99	0.66
Women	57 (82.6)	6 (100)	51 (81)	0.24
Menopause	38 (55.1)	6 (100)	32 (50.8)	0.16
Duration of menopause (year)	2 (0–41)	14 (7–34)	1 (0–41)	0.03
RA disease duration (year)	13.59 \pm 8.73	14.33 \pm 11.57	13.52 \pm 8.53	0.83
RF positivity	61 (88.4)	6 (100)	55 (87.3)	1.00
DAS28CRP	2.61 \pm 1.15	3.49 \pm 1.61	2.53 \pm 1.07	0.05
HAQ	0 (0–2.13)	0.63 (0–1.75)	0 (0–2.13)	0.27
Duration of GCs (months)	6.06 \pm 5.78	4.42 \pm 4.41	6.23 \pm 5.90	0.47
Cumulative dose of GCs (g)	9.49 (0–60.23)	8.94 (0.04–21.9)	9.73 (0–60.23)	0.75
History of osteoporosis	27 (39.1)	3 (50)	24 (38.1)	0.67
Previous non-VFs	7 (10.1)	3 (50)	4 (6.3)	0.01
History of osteoporosis drug use	10 (14.5)	0 (0)	10 (15.9)	0.58
Use of calcium	49 (71)	6 (100)	43 (68.3)	0.17
Use of vitamin D	48 (69.6)	6 (100)	42 (66.7)	0.17
BMD (g/cm ²):				
Lumbar spine BMD	0.817 \pm 0.156	0.655 \pm 0.092	0.833 \pm 0.152	<0.01
Femoral neck BMD	0.682 \pm 0.105	0.585 \pm 0.091	0.691 \pm 0.102	0.02
Forearm BMD	0.571 \pm 0.118	0.421 \pm 0.097	0.585 \pm 0.111	<0.01
TBS	1.328 \pm 0.104	1.341 \pm 0.086	1.327 \pm 0.106	0.75
TBS groups:				
TBS \leq 1.310	29 (42)	3 (50)	26 (41.3)	0.69
TBS $>$ 1.310	40 (58)	3 (50)	37 (58.7)	0.69
MOF-FRAX without BMD (%)	3 (0.6–19)	8 (2.1–16)	2.5 (0.6–19)	0.02
HF-FRAX without BMD (%)	0.5 (0.1–12)	2.85 (0.5–7.2)	0.4 (0.1–12)	0.01
MOF-FRAX with BMD (%)	3.2 (0.7–23)	7.7 (2.5–22)	2.6 (0.7–23)	0.01
HF-FRAX with BMD (%)	0.7 (0–16)	2.85 (0.6–12)	0.6 (0–16)	0.01
MOF-FRAX/TBS (%)	2.9 (0.2–22)	7.75 (1.9–22)	2.9 (0.2–21)	0.03
HF-FRAX/TBS (%)	0.6 (0–12)	2.6 (0.2–11)	0.4 (0–12)	0.03

BMI, body mass index (weight/height²); RF, rheumatoid factor; DAS28CRP, disease activity score 28 with CRP; HAQ, health assessment questionnaire; GCs, glucocorticoids; BMD, bone mineral density; TBS, trabecular bone score. FRAX, fracture risk assessment tool; MOF-FRAX, 10-year probability of major osteoporotic fracture by FRAX tool; HF-FRAX, 10-year probability of hip fracture by FRAX tool; MOF-FRAX/TBS, 10-year probability of major osteoporotic fracture by FRAX tool adjusted to TBS; HF-FRAX/TBS, 10-year probability of hip fracture by FRAX tool adjusted to TBS.

p expressed the difference between RA patients with and without VFs. It was significant when ≤ 0.05 .

with a predominance of the thoracic spine (66.67 %). Five fractures occurred in osteoporosis, one in osteopenia, and no fractures occurred in normal BMD.

The mean age of the subjects with VFs (63.17 ± 11.72 years) was numerically higher than that of subjects without VFs (55.57 ± 9.72 years, $p = 0.08$), and their disease activity was also higher. Values of BMD of the lumbar spine, femoral neck, and forearm were significantly lower in subjects with VFs.

The univariate logistic analysis revealed no association between TBS and vertebral fractures. This finding remained consistent even after adjustment for a model based on DAS28CRP, HAQ, body mass index, and glucocorticoid use duration in months (**Tables 2 and 3**). All the FRAX scores were positively associated with VFs in the univariate and multivariate analysis.

3.1. Fracture discrimination using BMD, TBS, and FRAX scores

The area under the curve (AUC) values for detecting vertebral fractures were 0.515, 0.212, and 0.151 for TBS, femoral neck BMD, and lumbar spine BMD, respectively. However, both FRAX with and without BMD demonstrated higher AUCs than TBS and TBS-adjusted FRAX. Additionally, FRAX with BMD exhibited better discrimination than FRAX without BMD (**Fig. 1**). Although TBS-adjusted FRAX scores had a reasonable AUC in predicting previous non-vertebral fractures (MOF = 0.817/ HF = 0.835), TBS alone was unable to discriminate such fractures (AUC = 0.507). The best discrimination was achieved by HF-FRAX without BMD for non-vertebral fractures (AUC = 0.915).

4. Discussion

In the present study, the majority of RA patients with VFs had normal vertebral TBS compared with those without VFs, whereas osteoporotic patients had more vertebral fractures than non-osteoporotic patients. TBS showed no association with prevalent vertebral fractures in our RA patients, whereas the FRAX score demonstrated such an association. The MOF-FRAX with BMD was the best parameter for predicting vertebral fractures.

The FRAX tool incorporates risk factors associated with femoral neck BMD. These clinical risk factors include age, height, weight, gender, smoking, alcohol use, glucocorticoid use, and history of secondary osteoporosis. Its use to estimate individual fracture risk in patients with RA with or without BMD has been the subject of considerable debate and research interest.

A study conducted in China (**Meng et al., 2017**) suggested that the FRAX model should include femoral neck BMD to become a valuable screening tool for assessing the risk of osteoporotic fracture in patients with RA. Previous research has already established that the FRAX tool, with or without BMD, is a strong predictor of patients at risk of fracture. The inclusion of femoral neck BMD in the FRAX model facilitates the

Table 2
Univariate logistic regression with vertebral fractures as a dependent variable.

	OR	95 % IC	p
TBS	3.973	0.001–17,005.81	0.75
MOF-FRAX without BMD	1.198	1.016–1.412	0.03
HF-FRAX without BMD	1.266	0.958–1.674	0.09
MOF-FRAX with BMD	1.207	1.044–1.397	0.01
HF-FRAX with BMD	1.274	1.018–1.594	0.03
MOF-FRAX/TBS	1.185	1.034–1.358	0.01
HF-FRAX/TBS	1.299	1.026–1.644	0.03

TBS, trabecular bone score; FRAX, fracture risk assessment tool; MOF-FRAX, 10-year probability of major osteoporotic fracture by FRAX tool; HF-FRAX, 10-year probability of hip fracture by FRAX tool; MOF-FRAX/TBS, 10-year probability of major osteoporotic fracture by FRAX tool adjusted to TBS; HF-FRAX/TBS, 10-year probability of hip fracture by FRAX tool adjusted to TBS.

OR: odds ratio, IC: interval of confidence, significance of p value < 0.05 .

Table 3

Adjusted multivariate logistic regression on DAS28CRP, HAQ, BMI group, and glucocorticoids duration in months, with vertebral fractures as a dependent variable.

	OR	95 % IC	p
TBS	912.413	0.011- >50	0.24
MOF-FRAX without BMD	1.319	1.028–1.692	0.03
HF-FRAX without BMD	1.474	1.003–2.164	0.04
MOF-FRAX with BMD	1.304	1.052–1.616	0.01
HF-FRAX with BMD	1.403	1.054–1.867	0.02
MOF-FRAX/TBS	1.225	1.023–1.467	0.03
HF-FRAX/TBS	1.377	1.026–1.847	0.03

DAS28CRP, disease activity score 28 with CRP; HAQ, health assessment questionnaire, BMI group, body mass index group; TBS, trabecular bone score; FRAX, fracture risk assessment tool; MOF-FRAX, 10-year probability of major osteoporotic fracture by FRAX tool; HF-FRAX, 10-year probability of hip fracture by FRAX tool; MOF-FRAX/TBS, 10-year probability of major osteoporotic fracture by FRAX tool adjusted to TBS; HF-FRAX/TBS, 10-year probability of hip fracture by FRAX tool adjusted to TBS.

OR: odds ratio, IC: interval of confidence, significance of p value <0.05.

identification of patients at the highest risk for fracture and clinical intervention (Kanis et al., 2012). Similarly, in the CaMos study, the combination of FRAX and BMD was more effective in discriminating fractures than either FRAX or BMD alone (CaMos Research Group et al., 2011). Our study found that including BMD in the FRAX score significantly improves its association with vertebral fractures in RA patients. This finding is consistent with previous research and highlights the importance of considering BMD when identifying patients at risk of osteoporotic fractures.

The Trabecular Bone Score is a novel technique for predicting fragility fractures. TBS can be automatically calculated during a BMD measurement to provide additional information on trabecular characteristics that are not captured by bone density. A low TBS value indicates poor bone texture quality. This information could be particularly useful in cases of spinal degenerative disease where bone mineral density (BMD) is falsely elevated. Previous studies have demonstrated an association between TBS and fragility fractures in patients with type 2 diabetes (Choi et al., 2016; Dhaliwal et al., 2014) and primary hyperthyroidism (Romagnoli et al., 2013; Eller-Vainicher et al., 2013). This result was replicated in RA patients (Kim et al., 2016; Bréban et al.,

2012) demonstrating that TBS was as effective as BMD in detecting vertebral fractures. Furthermore, Choi Y.J. et al. (Choi et al., 2017) found that low TBS is associated with a higher risk of vertebral fractures, even after adjusting for confounding factors such as age, DAS28, and BMD. In this current study, TBS failed to detect VFs in our RA patients. Previous studies have included patients with rheumatoid arthritis without excluding common comorbidities such as diabetes, which may explain our results.

Our study found that FRAX scores were the most accurate in predicting prevalent VFs due to their integration of multiple variables, including previous fractures. In addition, unadjusted and BMD-adjusted FRAX scores were superior in predicting prevalent fractures compared to adjusted TBS-FRAX scores. Similarly, in a recent study, the FRAX score of major osteoporotic fracture showed the best ability to discriminate VFs in patients with systemic sclerosis and those with RA (Lee et al., 2023). It also concluded that TBS-adjusted FRAX showed no additional benefit in predicting vertebral fractures, compared with non-TBS-adjusted FRAX.

We could number some limitations in this study, notably the relatively small number of patients and the cross-sectional design, thus affecting VFs prevalence. The study sample was limited due to the applied exclusion criteria, which aimed to prevent biased results. Additionally, the number of patients with VFs deformities was relatively small as we only considered grade 2 or higher deformities to avoid overestimation. VFs screening consistency across studies is a question of debate (different means and measurement methods for VFs detection and grading deformities). This has impacted the observed VFs prevalence in the previous studies 10–15 % vs. 8.7 % in our study. In addition, the small sample size prevented us from performing subgroup analysis, so we could not analyze TBS associations within osteoporotic and osteopenic patients. However, the use of odds ratio as a statistical tool is appropriate when the phenomenon studied is rare. Finally, further studies in secondary osteoporosis and especially in RA are certainly needed to get closer to the place of TBS in patient subgroups.

In conclusion, TBS was not associated with VFs in our patients. However, FRAX scores were associated with VFs, and the MOF-FRAX score with BMD was the most effective in identifying prevalent VFs in RA patients.

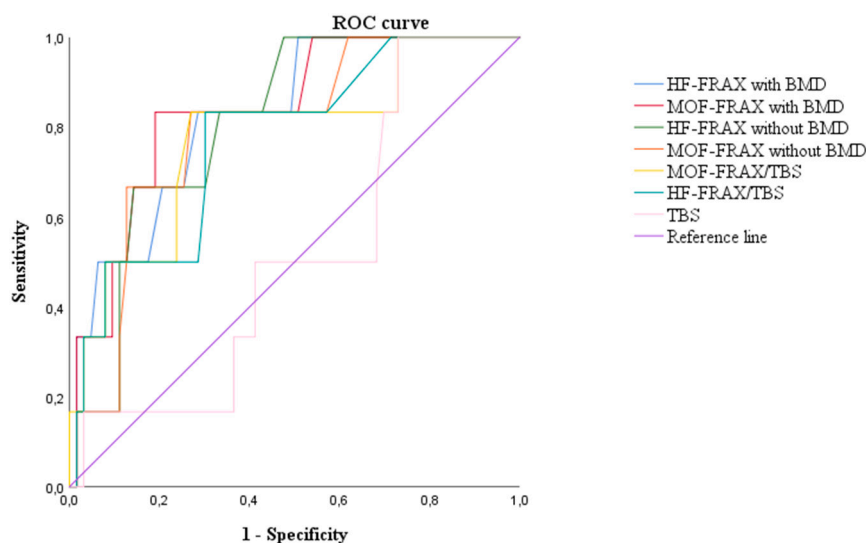


Fig. 1. Receiving Operator Characteristics (ROC) curves for MOF-FRAX with and without BMD, HF-FRAX with and without BMD, TBS, FRAX/HF-TBS, and MOF-FRAX/TBS in vertebral fracture detection. FRAX, fracture risk assessment tool; MOF-FRAX, 10-year probability of major osteoporotic fracture by FRAX tool; HF-FRAX, 10-year probability of hip fracture by FRAX tool; TBS, trabecular bone score; MOF-FRAX/TBS, 10-year probability of major osteoporotic fracture by FRAX tool adjusted to TBS; HF-FRAX/TBS, 10-year probability of hip fracture by FRAX tool adjusted to TBS.

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Compliance with ethics guidelines

The current study was approved by the local Ethics Committee of the Faculty of Medicine, Mohamed first university, Oujda, Morocco.

CRediT authorship contribution statement

Houssam Boutaibi: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Hamida Azzouzi:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Fadoua Chennouf:** Data curation. **Linda Ichchou:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Data availability

Data will be made available on request.

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