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Comparison of predictive value of FRAX, trabecular bone score, and bone mineral density for vertebral fractures in systemic sclerosis

A cross-sectional study

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Abstract

Assessing fracture risk is important for managing patients with systemic sclerosis (SSc). Vertebral fracture (VF) is the most common fracture and is associated with future VF and non-VF. We aimed to evaluate the predictive value of FRAX, trabecular bone score (TBS), and bone mineral density (BMD) for VFs, compared to rheumatoid arthritis (RA) patients and postmenopausal women, and to identify risk factors for VFs in SSc. In this cross-sectional study, prevalent VFs, 10-year probability of major osteoporotic fracture by FRAX (FRAX-MOF), TBS, and BMD were assessed in women with SSc (n = 69) and RA (n = 58), and postmenopausal women (n = 38). Risk factors for osteoporosis, modified Rodnan total skin score (mRSS), organ involvement, and patterns of nailfold capillaroscopy (NFC) were also evaluated. The accuracy of BMD (T-score ≤ −2.5), TBS and FRAX-MOF, with and without TBS adjustment, to detect prevalent VF was assessed by determining the area under the receiver operating characteristic (ROC) curve. Patients with SSc (14.5%) and RA (17.2%) had significantly more VFs than postmenopausal women (0%) ($P = .031$). Non-significant differences were observed in TBS and BMD of all groups. The FRAX-MOF were higher in RA (9.2%) than SSc group (6.1%) and postmenopausal women (5.5%) ($P < .001$). Based on the ROC curve, TBS-adjusted FRAX-MOF (0.803) showed largest area under curve (AUC) to detect the prevalent VFs, followed by FRAX-MOF (0.796), TBS (0.765), and BMD (0.588) in the SSc group. In the RA group, FRAX-MOF had the largest AUC (0.896), followed by TBS-adjusted FRAX-MOF (0.863), TBS (0.736), and BMD (0.686). The cutoffs for FRAX-MOF and TBS-adjusted FRAX-MOF for detecting VFs were 8.95% and 9.7% for SSc, and 14.5% and 14% for RA. No association between VFs and SSc subtypes, organ involvement, mRSS or NFC patterns was found. FRAX-MOF, with or without TBS, had better predictive value for VFs than BMD and TBS in SSc. However, FRAX-MOF underestimated the probability of VFs in SSc compared with RA.

Abbreviations: aBMD = areal BMD, AUC = area under curve, BMD = bone mineral density, BMI = body mass index, CYC = cyclophosphamide, DXA = dual-energy X-ray absorptiometry, FRAX = fracture risk assessment tool, FRAX-HF = hip fracture by FRAX, FRAX-MOF = major osteoporotic fracture by FRAX, mRSS = modified Rodnan total skin score, NFC = nailfold capillaroscopy, RA = rheumatoid arthritis, ROC = receiver operating characteristic, SSc = systemic sclerosis, TBS = trabecular bone score, VF = vertebral fracture.

Keywords: bone, bone density, cancellous bone, fractures, osteoporosis, scleroderma, systemic

1. Introduction

Osteoporosis is a common comorbidity in patients with systemic sclerosis (SSc). Multiple factors such as immobility, malabsorption, and premature ovarian failure due to use of cyclophosphamide (CYC) and glucocorticoids, persistent inflammation and result in bone loss, thereby contributing to development of osteoporosis in patients with SSc.[1–3]

Previous studies report higher prevalence of fractures among SSc patients than healthy controls.[4–8] Assessing fracture risk is important for managing SSc patients. Bone mineral density (BMD), measured using dual-energy X-ray absorptiometry (DXA), is the gold standard for evaluation of osteoporosis. Trabecular bone score (TBS) determines the bone microarchitecture, and is an independent risk factor for osteoporotic fractures.[9]

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Clinical risk factors such as advanced age, female sex, GC use, and a history of osteoporotic fractures predict fragility fractures, independent of BMD. Vertebral fracture (VF) is the most common fracture and is associated with future VF and non-VF. The fracture risk assessment tool (FRAX) is an algorithm, widely used for predicting the risk and occurrence of major osteoporotic fractures (MOF) and hip fractures (HF) in 10 years. This FRAX-MOF and FRAX-HF can be adjusted using the TBS. In rheumatoid arthritis (RA), osteoporosis and fragility fracture risk assessment, including clinical risk factors, DXA, and FRAX are recommended.[10] However, the predictive value of the FRAX tool, BMD, and TBS for osteoporotic fracture has not been validated in SSc patients.

This study aimed to evaluate the predictive value of the fracture risk assessment tool, including BMD, TBS, and FRAX, with and without TBS adjustment in SSc patients, compared to RA patients and postmenopausal women, and to identify risk factors related to prevalent VFs in SSc.

2. Materials and methods

2.1. Study participants

This cross-sectional study was conducted at a secondary hospital located in South Korea between July 2019 and December 2021. Women diagnosed with SSc were enrolled as test subjects, while those diagnosed with RA and postmenopausal women were enrolled as control subjects. SSc and RA were definitively diagnosed in accordance with the 2013 American College of Rheumatology/European League against Rheumatism classification criteria[11] and the 2010 American College of Rheumatology/European League against Rheumatism classification criteria,[12] respectively. Postmenopausal women were recruited through advertising (brochures, and posters). Age < 40 years, rheumatic diseases other than SSc and RA, premenopausal status, chronic liver or renal disease, thyroid or parathyroid diseases, gastrectomy, bariatric surgery, and chronic obstructive pulmonary disease comprised the exclusion criteria. This study adhered to the principles of Declaration of Helsinki, and was approved by the Institutional Review Board for Human Research (study number: 2020-10-008). Written consent was obtained from all participants.

2.2. Clinical and laboratory evaluation

The following baseline characteristics were recorded for each subject: demographics; disease duration; and risk factors of osteoporosis. The daily and cumulative GC doses, use of immunosuppressive agents and medications for osteoporosis were recorded. History of non-VFs (excluding fracture of digits, and pathological and non-minimal trauma fractures) and symptomatic VFs was collected from self-reported questionnaires and medical chart reviews.

Laboratory tests were performed to determine levels of 25 hydroxyvitamin D, serum procollagen type 1 intact N-terminal propeptide, and C-terminal telopeptide of type 1 collagen. The presence of anti-centromere and anti-topoisomerase was also evaluated.

Additionally, SSc-specific internal organ involvement including interstitial lung disease, gastrointestinal involvement,[13] scleroderma renal crisis,[14] and pulmonary arterial hypertension, was investigated.[15] The skin thickness score was calculated using the modified Rodnan total skin score (mRSS).[16] Patterns of nailfold capillaroscopy (NFC) were obtained for patients with SSc, as early, active and late patterns.[17]

2.3. Identifying prevalent VF

Prevalent VF, which is the strongest risk factor for future fractures,[18] was evaluated by a radiologist using radiographs of the thoracic and lumbar spine. VF was defined as a reduction of 20% or more in the anterior, posterior, and/or middle vertebral height, compared to the adjacent, undeformed vertebral body.[19,20]

2.4. TBS and aBMD assessment

The areal BMD (aBMD) was measured at the lumbar spine (L1-L4) and left hip (femoral neck and total proximal femur) using DXA (Hologic Horizon W; Hologic Inc., Danbury, CT). TBS was evaluated at the lumbar spine (L1–L4) on the same DXA acquisition used for aBMD assessment using the TBS iNsight software (version 3.0; Med-Imaps, Merignac, France). All fractured lumbar vertebrae were excluded in lumbar BMD and TBS.

2.5. Osteoporotic fracture risk evaluation by FRAX

We calculated FRAX values using the Korean model (http://www.shef.ac.uk/FRAX/tool.aspx?country=25). The 10-year probabilities of major osteoporotic fracture (FRAX-MOF) and hip fracture (FRAX-HF) were calculated using the FRAX tool with femoral neck BMD. TBS-adjusted FRAX-MOF and FRAX-HF were also calculated.

2.6. Statistical analysis

Statistical analyses were performed using SPSS software (ver. 22.0; IBM, Armonk, NY) and Rex (version 3.6.0; Rexsoft Inc., Seoul, Korea). Continuous variables are expressed as mean (SD) or median (Q1, Q3), and categorical variables are presented as numbers (%). Differences among the three groups were analyzed using the Kruskal–Wallis test followed by Bonferroni post hoc test. Data was compared using the chi-square test and Mann–Whitney *U* test, as appropriate. Furthermore, the accuracy of BMD (T-score ≤ –2.5), TBS and FRAX-MOF, with and without TBS adjustment, to detect prevalent VF was assessed by determining the area under the receiver operating characteristic (ROC) curve. Comparison of ROC curves by bootstrap analysis was also performed between the SSc and RA groups. For all analyses, results were considered statistically significant at $P < .05$.

3. Results

3.1. Baseline characteristics of the enrolled patients

A total of 165 patients were included in the study: SSc (n = 69), RA (n = 58), and postmenopausal women (n = 38). The baseline characteristic of the study population are shown in Table 1. The SSc group comprised of subjects with limited cutaneous SSc (n = 37) and diffuse cutaneous SSc (n = 32). Significantly lower cumulative GC intake was observed in SSc group, when compared with the RA group ($P < .001$). However, the daily dose between both groups remained comparable. The use of bisphosphonate and calcium replacement was higher in the RA patients than in the SSc patients and postmenopausal women ($P = .019$ and $P < .001$, respectively).

3.2. Assessment of prevalent VFs, BMD, TBS, and FRAX

Patients with SSc (14.5%) and RA (17.2%) had significantly more prevalent VFs than postmenopausal women (0 %) ($P = .031$) (Table 2). However, no significant differences were observed in aBMD at the lumbar spine, femoral neck, or total hip, and TBS at the lumbar spine among the three groups. There was no difference in prevalent VFs between SSc and RA groups. Median FRAX-MOF and FRAX-HF were higher in the RA group (9.2% and 2.7 %, respectively) than in the SSc group (6.1% and 1.4 %, respectively) and postmenopausal women (5.5% and 1.8 %, respectively). After adjustment with TBS, the FRAX-HF were equal to or lower than those without TBS in all

Table 1

Characteristics of the study population.

	SSc (n = 69)	RA (n = 58)	Postmenopausal women (n = 38)	*P* value
Age, yr	61.1 (7.7)	63.2 (8.7)	59.8 (8.2)	.188
Female, n (%)	62 (89.8)	52 (89.6)	38 (100)	.551
BMI, kg/m^2	22.9 (2.3)	22.7 (3.6)	22.4 (2.8)	.082
Disease duration, yr, median (Q1, Q3)	2.9 (0.7, 5.0)	3.8 (2.1, 6.4)	–	.640
Current smoking, n (%)	4 (5.7)	7 (12.1)	1 (2.6)	.088
Alcohol ≥ 3 U/d, n (%)	0 (0)	0 (0)	1 (2.6)	.143
Diabetes mellitus, n (%)	3 (4.3)	6 (10.3)	3 (7.8)	.509
Previous symptomatic VFs, n (%)	3 (4.3)	6 (10.3)	0 (0)	.085
Previous non-VFs, n (%)	5 (7.2)	6 (10.3)	0 (0)	.140
Family history of osteoporotic facture, n (%)	2 (2.8)	2 (3.4)	1 (2.6)	.074
Cumulative GC dose, mg	2516.3 (3219.8)	4240.5 (3966.2)	-	<.001
Current GC dose at time of BMD, mg/d	2.3 (2.4)	3.0 (2.2)	-	.085
Laboratory tests				
25(OH)D, ng/mL	19.9 (10.0)	24.3 (14.0)	25.0 (51.3)	.078
CTX, ng/mL	0.37 (0.20)	0.35 (0.19)	0.37 (0.21)	.706
P1NP, ng/mL	45.8 (26.1)	40.9 (25.1)	53.6 (21.6)	.076
Medication				
Bisphosphonate, ever, n (%)	11 (15.9)	18 (31.0)	3 (7.8)	.019
SERM, n (%)	11 (15.9)	11 (18.9)	8 (21.1)	.805
Vitamin D, n (%)	30 (43.4)	35 (60.3)	16 (42.1)	.195
Calcium, n (%)	5 (7.2)	23 (39.6)	2 (5.3)	<.001

Data are presented as the mean (SD), unless otherwise stated.

(OH)D = 25-hydroxy vitamin D3, BMD = bone mineral density, BMI = body mass index, CTX = C-terminal cross linking telopeptide of type 1 collagen, GC = glucocorticoid, P1NP = Procollagen 1 N-terminal propeptide, RA = rheumatoid arthritis, SERM = selective estrogen receptor modulator, SSc = systemic sclerosis, VF = vertebral fracture.

Table 2

Parameters associated with osteoporotic fracture in SSc, RA, and postmenopausal women.

					Post hoc analysis*		
	SSc (n = 69)	RA (n = 58)	Postmenopausal women (PW) (n = 38)	*P* value	*P* value (SSc vs RA)	*P* value (SSc vs PW)	*P* value (RA vs PW)
Vertebral fracture, n (%)	10 (14.5)	10 (17.2)	0 (0)	**.031**	1.000	**.039**	**.018**
Lumbar spine aBMD, g/cm^2	0.82 (0.11)	0.84 (0.11)	0.85 (0.13)	.944			
Lumbar spine, T-score	–2.11 (1.04)	–1.93 (0.99)	–1.81 (1.18)	.338			
Femoral neck aBMD, g/cm^2	0.63 (0.10)	0.62 (0.11)	0.63 (0.09)	.079			
Femoral neck, T-score	–1.98 (0.94)	–2.05 (0.95)	–1.93 (0.80)	.817			
Total hip aBMD, g/cm^2	0.76 (0.12)	0.74 (0.12)	0.76 (0.10)	.239			
Total hip, T-score	–1.51 (–1.01)	–1.64 (0.98)	–1.48 (0.81)	.680			
Lumbar spine TBS	1.34 (0.07)	1.35 (0.07)	1.37 (0.06)	.143			
FRAX-MOF, median (Q1, Q3)	6.1 (4.5, 10.0)	9.2 (5.8, 17.0)	5.5 (4.6, 8.1)	**<.001**	**.003**	.759	**<.001**
FRAX-HF, median (Q1, Q3)	1.4 (0.9, 4.1)	2.7 (1.2, 7.1)	1.8 (0.8, 2.8)	**.007**	**.033**	1.000	**.015**
FRAX-MOF with TBS, median (Q1, Q3)	5.9 (4.0, 10.0)	7.9 (5.3, 16.5)	5.5 (4.1, 8.7)	**.008**	.069	.750	**.012**
FRAX-HF risk with TBS, median (Q1, Q3)	1.1 (0.7, 3.8)	2.2 (0.8, 6.3)	1.0 (0.5, 2.7)	**.046**	.264	.897	.057

Data are presented as the mean (SD), unless otherwise stated.

aBMD = areal bone mineral density, FRAX-HF = 10-year probability of hip fracture by fracture risk assessment tool, FRAX-MOF = 10-year probability of major osteoporotic fracture by fracture risk assessment tool, RA = rheumatoid arthritis, SSc = systemic sclerosis, TBS = trabecular bone score.

*Adjusted *P* values corrected by Bonferroni adjustment are presented.

three groups. FRAX-MOF adjusted with TBS was also higher in the RA group than in the control group.

3.3. Accuracy of BMD, TBS, and FRAX-MOF with and without TBS to detect prevalent VF

Using the ROC curve, FRAX-MOF adjusted with TBS depicted the highest area under the curve (AUC), followed by FRAX-MOF without TBS adjustment, TBS, and BMD (T-score ≤ –2.5) in patients with SSc (Fig. 1). The optimal cut-offs, producing the best sensitivity and specificity for FRAX-MOF, FRAX-MOF with TBS and TBS, were 8.95%, 9.7%, and 1.273%, respectively. FRAX-MOF adjusted with TBS slightly increased the AUC from 0.796 (95% CI, 0.619–0.957) to 0.803 (95% CI, 0.616–0.941). However, this difference was not statistically significant. Osteoporosis based on BMD

(T-score ≤ –2.5 at any site) was not significantly different from 0.5, when assessing VF.

In RA group, FRAX-MOF showed the highest AUC (0.896 [95% CI, 0.811–0.972]) to detect the prevalent VFs, followed by TBS-adjusted FRAX-MOF, TBS, and BMD (T-score ≤ –2.5). The optimal cutoffs, producing the best sensitivity and specificity for FRAX-MOF, FRAX-MOF with TBS and TBS, were 14.5%, 14% and 1.329%, respectively. TBS-adjusted FRAX (0.863 [95% CI, 0.703–0.983]) decreased the AUC compared with FRAX-MOF. Similar to SSc group, BMD (T-score ≤ –2.5) as a single assessment did not show any discriminative ability for VF. Based on the AUC, the discriminative ability of FRAX-MOF and FRAX-MOF with TBS for VF was higher in patients with RA than in those with SSc, but the difference was not statistically significant.

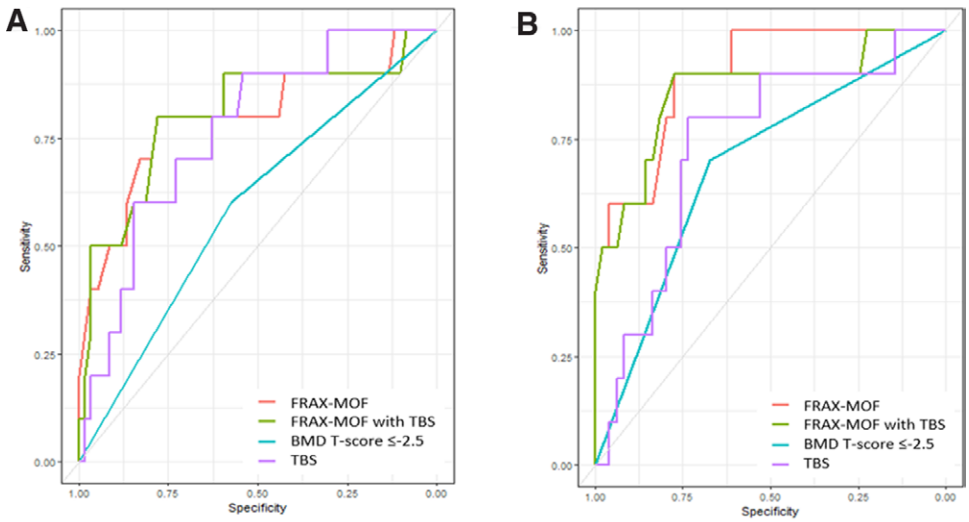
3.4. Characteristics of SSc patients with and without VFs

Table 3 shows the clinical and laboratory characteristics of patients with SSc, with and without VFs. Prevalence of VFs was higher among older SSc patients, and those taking higher doses of glucocorticoids, but this was not statistically significant. There were no significant differences between SSc patients with and without VFs with respect to body mass index (BMI), smoking status, alcohol consumption, history of non-VFs, disease duration, SSc subtypes, internal organ involvement, mRSS, NFC patterns, autoantibody profiles, and the use of immunosuppressive agents. TBS was significantly lower in SSc patients with VFs. However, aBMD and osteoporosis according to T-score (≤ –2.5) were comparable between the two groups. FRAX-MOF and FRAX-HF with and without adjusted TBS were significantly higher in SSc patients with VFs than in those without VFs.

4. Discussion

This study compared the predictive value of BMD, TBS, and FRAX with and without TBS adjustment, for detecting VFs in patients with SSc and RA, and postmenopausal women. The prevalence of VFs was higher in SSc and RA patients than in postmenopausal women, but the aBMD and T-score, based on DXA and TBS, were comparable among all groups. Previous studies have reported age, BMI, and vitamin D deficiency as risk factors of osteoporosis in patients with SSc.[6,21] Statistically non-significant differences were observed in BMI and 25 hydroxyvitamin D levels among all groups. Inclusion of subjects on prior medications for osteoporosis, like bisphosphonate vitamin D and calcium replacement, may justify similar BMD and TBS values among all groups.

Despite similar VF prevalence between groups, the SSc group exhibited lower FRAX-MOF and FRAX-HF than the RA group. VFs were not reported in postmenopausal women, but their FRAX-MOF and FRAX-HF were comparable to those of patients with SSc. Our study suggested an underestimation of FRAX probabilities in the SSc groups. The National Osteoporosis Foundation recommends pharmacological intervention for postmenopausal women, and men aged above 50 years, with history of HF or VF, BMD-based osteoporosis (T-score ≤ –2.5), FRAX-MOF ≥ 20%, or FRAX-HF ≥ 3%.[22] A recent study also reported that FRAX and TBS-adjusted FRAX in patients with SSc did not result in any new indications for therapeutic intervention.[23] This study reported the cutoffs for VF predictions, using FRAX-MOF and TBS-adjusted FRAX-MOF, as 8.95% and 9.7% in SSc and 14.5% and 14.0% in RA, respectively. A recent Korean cohort-based study suggested an optimal threshold of FRAX 10-year probabilities for MOF as 7.2% in postmenopausal women. Japan uses 15% 10-year probability of MOF as intervention threshold.[24] In addition to geo-epidemiology, distinct disease characteristics can affect



Vertebral fracture	AUC (95% CI)	P-Value
FRAX-MOF	0.795 (0.619-0.957)	0.003
FRAX-MOF with TBS	0.803 (0.616-0.941)	0.002
BMD T-score≤ -2.5	0.588 (0.616-0.941)	0.375
Lumbar spine TBS	0.765 (0.624-0.892)	0.008

Systemic sclerosis

Vertebral fracture	AUC (95% CI)	P-Value
FRAX-MOF	0.896 (0.811-0.972)	<0.001
FRAX-MOF with TBS	0.863 (0.703-0.983)	<0.001
BMD T-score≤ -2.5	0.686 (0.542-0.852)	0.065
Lumbar spine TBS	0.736 (0.544-0.883)	0.019

Rheumatoid arthritis

Figure 1. ROC curves of BMD, L-spine TBS, and 10-year probability of major osteoporotic fracture (MOF) by the FRAX tool, with and without adjustment of TBS in VF identification. (A) Patients with systemic sclerosis (10 patients with VF of 69 patients). (B) Patients with rheumatoid arthritis (10 patients with VF of 58 patients). BMD = bone mineral density, FRAX = fracture risk assessment tool, FRAX-MOF = 10-year probability of major osteoporotic fracture by FRAX, FRAX-MOF with TBS = 10-year probability of major osteoporotic fracture by FRAX adjusted by TBS, RA = rheumatoid arthritis, ROC = receiver operating characteristic, TBS = trabecular bone score, VF = vertebral fracture.

Table 3

Characteristics associated with vertebral fractures in patients with SSc.

Characteristics	With VF (n = 10)	Without VF (n = 59)	*P* value
Age, yr	71 (63, 78)	61 (55.5, 65)	.002
Female, n (%)	9 (90)	53 (89.8)	1.000
BMI	23.1 (22.6, 23.8)	22.7 (21.4, 24.4)	.181
Non-vertebral fractures, n (%)	2 (20)	8 (13.6)	.150
Clinical characteristics			
Diffuse cutaneous SSc, n (%)	3 (30)	29 (49.1)	.701
Disease duration	36.5 (17.2, 52.7)	18 (5.75, 30.5)	.247
Modified Rodnan skin score	6 (3.5, 9)	8 (4, 13)	.171
ILD, n (%)	7 (70)	38 (64.4)	1.000
PAH, n (%)	1 (10)	3 (5.1)	.452
GI involvement, n (%)	7 (70)	31 (52.5)	.435
Digital ulcer, n (%)	2 (20)	8 (13.5)	.590
NFC*	2 (1, 3)	2 (1, 3)	.663
Laboratory tests			
Anti-centromere, n (%)	6 (60)	29 (49.1)	.710
Anti-topoisomersae, n (%)	2 (20)	12 (20.3)	1.000
25(OH)D, ng/mL	18.4 (16.5. 27.3)	18.8 (13.6, 27.5)	.520
Medication			
Cumulative GC dose, mg	3525 (927, 4705)	1007.5 (0, 3360)	.086
GC dose at time of BMD, mg	2.5 (2.5, 5.0)	2.5 (0, 2.5)	.052
Bisphosphonates, ever, n (%)	2 (20)	9 (15.2)	1.000
Vitamin D, n (%)	4 (40)	26 (44.1)	1.000
Cyclophosphamide, n (%)	2 (20)	12 (20.3)	1.000
Mycophenolate mofetil, n (%)	4 (40)	24 (40.6)	1.000
TBS, L1-4	1.255 (1.228, 1.315)	1.349 (1.31, 1.398)	.008
Lumbar spine aBMD, g/cm^2	0.819 (0.667, 0.857)	0.83 (0.772, 0.899)	.344
Femoral neck aBMD, g/cm^2	0.552 (0.537, 0.617)	0.645 (0.602, 0.702)	.107
Total hip aBMD, g/cm^2	0.707 (0.595, 0.746)	0.791 (0.708, 0.871)	.044
Osteoporosis according to T score (≤−2.5), n (%)	6 (60)	25 (42.3)	.327
FRAX 10-year MOF risk	17 (12.9, 20)	5.5 (4.5, 7.6)	.003
FRAX 10-year HF risk	6.7 (4.1, 8.9)	1.2 (0.8, 2.3)	.003
FRAX 10-year MOF risk with TBS	17 (12.9, 20)	5.6 (3.7, 8.4)	.002
FRAX 10-year HF risk with TBS	6.8 (4.6, 8.6)	1.0 (0.6, 2.4)	.002

Data are presented as the median (Q1, Q3) unless otherwise stated.

aBMD = areal bone mineral density, BMI = body mass index, CYC = cyclophosphamide, FRAX-HF = 10-year probability of hip fracture by fracture risk assessment tool, FRAX-MOF = 10-year probability of major osteoporotic facture by fracture risk assessment tool, GC = glucocorticoid, SSc = systemic sclerosis, TBS = trabecular bone score.

*1, early pattern; 2, active pattern; 3, late pattern.

FRAX probabilities. To overcome underestimation of the FRAX tool in SSc, development of an adjusted FRAX probability for SSc, or modification of the cutoff threshold of FRAX probabilities requiring anti-osteoporotic treatment, is needed.

FRAX-MOF showed the best discriminative capacity, followed by TBS, in the SSc and RA groups. However, osteoporosis based on BMD (T-score ≤ –2.5) using DXA revealed poor discrimination for VFs in both groups. Some studies have reported similar findings, stating that BMD is not an independent predictor of osteoporotic fractures in the RA population.[18,25] The incidence of degenerative diseases increases with age. Overestimation of BMD can occur due to age-related degenerative changes, such as osteophytes.[26] In the present study, patients with prevalent VFs were significantly older than those without VFs in both the SSc (71.0 vs 61.0 years, respectively) (*P* = .002) and RA groups (72.5 vs 60.0 years, respectively) (*P* = .001). The Osteolaus cohort showed no effect of degenerative disease on the continually declining TBS, and an increased BMD after the age of 62.5 years.[27] Moreover, previous studies have reported better discriminative ability of TBS for fracture risk assessment than BMD in patients on chronic GC therapy, even at low doses.[20,28] GC therapy has a greater negative effect on trabecular bone than on cortical bone.[29] Inclusion of 60% and 76.2% GC-treated patients in SSc and RA groups, respectively, reveals that, GC usage and advanced age may have affected the lower VF predictive ability of BMD in present study.

Although we demonstrated that prevalent VFs were associated with low TBS, VF prediction by TBS-adjusted FRAX did not show an additional benefit, compared to FRAX without TBS in patients with SSc and RA. Some studies have shown that TBS has additional value in predicting osteoporotic fractures in postmenopausal women and older men.[30,31] Contrastingly, a recent community-based cohort study reported that compared to the clinical risk factor-based FRAX in Korean women, FRAX with TBS or BMD adjustment did not improve the predictive value for MOF, and raised lower FRAX probabilities in the Koreans than in the Caucasians and Japanese patients.[32] Thus, international collaborative studies, determining additional value of TBS-adjusted FRAX in patients with SSc are warranted.

This study also identified the risk factors of prevalent VF in patients with SSc. We found no association of TBS with SSc subtype, and internal organ involvement pattern, which was consistent with a previously reported study.[8] Ruaro et al reported that SSc patients with late NFC pattern had lower TBS than those with early or active NFC pattern. However, we observed no significant associations between VFs and NFC patterns. CYC is one of the therapeutic regimens that has been widely used in clinical practice in patients with SSc. However, CYC is related to premature ovarian failure, and suppressive effect of CYC on osteoblastogenesis has been shown in an animal study.[2,33] This raises concerns about the development of osteoporotic fracture in patients with SSc. The present study did not form an association between immunosuppressive agents and the prevalence of VFs in patients with SSc. Among the CYC users in our SSc patients, 71.4% of patients were postmenopausal at the time of CYC treatment, and 14.3% of patients were male sex. Postmenopausal status at CYC administration or immune modulatory effect of CYC may have affected our results.

Present study had several limitations. This study had a cross-sectional design, and a causal relationship between current fracture risk assessment and future fractures could not be determined. Indeed, the sample size of patients with SSc and prevalent VFs were relatively small. Further large-scale prospective cohort study is required to confirm our findings.

5. Conclusions

This study reports better VF predictive capacity of FRAX-MOF, with or without TBS, than of BMD and TBS in patients with SSc. The prevalence of VFs was comparable between SSc and RA groups, FRAX-MOF underestimated the probability of VFs in SSc compared with RA. SSc-specific risk factors for VFs, including SSc subtypes, mRSS, internal organ involvement, and NFC features, were not found. For the application of FRAX in clinical practice, the development of adjusted FRAX probabilities or threshold modifications is needed in patients with SSc.

Author contributions

KAL, HJK, and HSK were involved in study conception and design. KAL was involved in data acquisition. KAL and HSK performed data analysis and interpretation. All authors were involved in the drafting or critical revision of the article, and all authors approved the final version for publication. HSK had full access to all of the data in the study and takes.

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