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ORIGINAL ARTICLE

The use of pulse-echo ultrasound in women with a recent non-vertebral fracture to identify those without osteoporosis and/or a subclinical vertebral fracture: a pilot study

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Abstract

Summary A pilot study on the use of P-EU to identify patients without osteoporosis and/or a subclinical vertebral fracture after a recently sustained non-vertebral fracture (NVF).

Introduction Screening with portable devices at emergency departments or plaster rooms could be of interest to limit referrals for dual X-ray absorptiometry (DXA) and vertebral fracture assessment (VFA). We calculated the number of negative tests for osteoporosis and/or subclinical vertebral fractures (VFs) using pulse-echo ultrasonometry (P-UE) at different thresholds.

Patients and methods In this cross-sectional study, 209 consecutive women of 50–70 years with a recent non-vertebral fracture (NVF) were studied at the Fracture Liaison Service (FLS) of one hospital. All women received DXA/VFA and P-EU (Bindex®) assessments. Various P-EU thresholds (based on the density index (DI, g/cm^2)) were analyzed to calculate the best balance between true negative (indeed no osteoporosis and/or subclinical VF) and false negative tests (osteoporosis and/or subclinical VF according to DXA/VFA).

Results Eighty-three women had osteoporosis (40%) and 17 women at least one VF (8%). Applying the manufacturer's recommended P-EU threshold (DI 0.844 g/cm^2) being their proposed cut-off for not having hip osteoporosis resulted in 77 negative tests (37%, 31% true negative and 6% false negative tests). A DI of 0.896 g/cm^2 resulted in 40 negative tests (19.3%) (38 true negative (18.3%) and 2 false negative tests (1.0%)).

Conclusion The application of P-EU enables the identification of a substantial proportion of women with recent non-vertebral fractures at the FLS who would not need a DXA/VFA referral because they had no osteoporosis and/or subclinical vertebral fractures. The most conservative P-EU threshold resulted in 18.3% true negative tests verified by DXA/VFA against 1% false negative test results.

Keywords DXA/VFA · FLS · Non-vertebral fracture · Osteoporosis · Subclinical vertebral fracture · Pulse-echo ultrasound

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Introduction

The burden of osteoporotic fractures increases worldwide due to aging and the contribution of the subsequent in part preventable fractures [1–3]. Osteoporotic fractures not only represent a large disease burden but it is also associated with increased mortality [4, 5]. Secondary fracture prevention care is considered to be best organized at a Fracture Liaison Service (FLS) [6], and this is therefore propagated by the International Osteoporosis Foundation, the ASBMR, and EULAR/EFORT [1, 3, 7]. However, a substantial work-up and treatment gap still remains due to limited or even low attendance rates [8]. Lack of recalled patient information (extrinsic motivation) and lack of patient's interest in personal health issues (intrinsic motivation) have been shown to be

major clues for FLS non-attendance [9–12]. Screening for the presence of osteoporosis with peripheral devices in patients with a fracture intending to improve the proportion of patients that get further analyzed and treated with anti-osteoporosis medication has been previously highlighted but did not yet result in guidelines worldwide [12]. Fast track diagnosis and treatment shortly after the index fracture could be efficacious regarding subsequent fracture risk reduction in any fracture patient > 50 years [13]. Because of the imminent subsequent fracture risk [14, 15], it could be of added value to use a mobile peripheral screening imaging technique shortly after index fracture during fracture treatment procedures, on the one hand, to rule out patients with a "negative" screening test for having osteoporosis or prevalent subclinical VFs in order to reduce the number of DXA and VFA measurements and, on the other hand, to motivate, hence rule in, those with a "positive" screening test for further assessment at the FLS.

Screening at emergency departments and plaster rooms may be achievable and advantageous with peripheral portable non-ionizing ultrasound devices. Accuracy of quantitative ultrasound (QUS) in diagnosing osteoporosis as found by DXA has been reported in a number of studies [16, 17]. In a meta-analysis that explored the usability of QUS as a pre-screen stratification tool for the assessment of osteoporosis on DXA of the spine and hip, a wide range of supposed DXAscan savings ranging from 3 to 69% at the expense of false negative tests ranging from 0 to 12% was shown, depending on the screening strategy and study characteristics, device, measured variable, and cut-off values [18, 19]. In contrast to QUS, P-EU (Bindex®) measurements are performed at the proximal tibia and measures mainly cortical bone properties. In earlier studies, the P-EU outcomes showed reproducible good and significant correlation coefficient, between $r = 0.86$ and $r = 0.89$ with BMD at the femoral neck [20, 21]. Diagnostic accuracy studies using this device at a single site showed a specificity of 82% and a sensitivity of 80% for the detection of osteoporosis at the femoral neck or total hip [22, 23].

According to our knowledge, there are no data published on prescreening with QUS and/or P-EU in FLS cohorts and there are also no studies on prescreening with P-EU to predict subclinical VFs [16–18].

The rationale to use ultrasound to predict BMD—a different technique—is based on significant fracture prediction for both techniques [20–23]. However, DXA/VFA is the golden standard. Efficient and safe prediction of a negative test (i.e., low numbers of false negative tests) was held to be feasible in 50–70-year-old women with reference to subclinical vertebral fractures of 11% < 70 years versus 23% > 70 years [24, 25]. Besides, most data reported is in heterogeneous cohorts with or without previous fractures [20, 22].

Recently a handheld CE-approved pulse-echo ultrasonometer device (P-EU Bindex ®) that measures cortical thickness (CT) has been developed. The application of the P-EU Bindex® is based on the density index (DI), a composite value for sonographically measured cortical thickness (CTh) adjusted for age and body mass index (BMI) [20–22]. High prediction was reported for a DI threshold of 0.844 g/cm^2 to differentiate BMD femoral neck *t* scores below or above − 2.5 SD [22]. The NICE guideline on osteoporosis care recommends FRAX for fracture risk assessment [26, 27]. In case of a calculated risk above the threshold for intervention, a DXA including VFA is recommended. However, NICE leaves the application of Bindex® optional providing that it becomes adopted into NHS guidelines. In that scenario, Bindex could be used after FRAX as an adjunct tool to screen before DXA referral [27].

We aimed to study the number of avoidable DXA/VFA referrals applying different P-EU cut-off levels for DI. The approach was to calculate the proportion of DXA/VFAscan savings based on the calculated true as well as false negative tests per DI threshold in parallel. The study was performed in 50–70-year-old women who recently sustained a traumatic or non-traumatic NVF, a group considered to be at relatively low risk of osteoporosis and subclinical VFs [24, 25].

Patients and methods

A total of 591 consecutive women with a recent NVF and between 50 and 70 years were identified between September 1, 2016, and June 30, 2017, at the emergency department and plaster room of Reinier de Graaf Hospital, Delft, the Netherlands. After exclusion of women with toe, finger, and skull fractures, all women (except for women with fractures due to high-velocity traumata) were invited to attend the FLS both after exchanging patient information at the emergency and plaster room or outpatient clinic and in case of no attendance within 1 month by written invitation. As a pilot, we studied women between 50 and 70 years after recent fracture expecting their risk on osteoporosis and non-clinical vertebral fractures to be low [24, 25]. For this study, we excluded patients with clinical VFs since treatment is started in these patients regardless of the DXA outcome, according to the Dutch guideline [28].

DXA and vertebral fracture assessments (VFA) were standard clinical procedures in all FLS patients. For this study, women were separately asked permission for a P-EU (Bindex®) measurement. Patients and health care professionals had no insight into the outcome at the time of this measurement. Anti-osteoporosis treatment was recommended according to the Dutch guidelines (the presence of osteoporosis and/or a grade II/III subclinical prevalent VF) [28].

Index fractures were categorized in non-vertebral/non-hip minor, non-vertebral/non-hip major, hip, and VFs according to Warriner [29].

The study was carried out in accordance with good clinical practice (GCP; Medical Ethical Review Board: METC Zuidwest Holland; approval 16.190).

DXA and VFA

Patients had a DXA/VFA measurement (Hologic Discovery QDR®) at the lumbar spine, total hip, and femoral neck, and a VFA. Osteoporosis was defined according to the WHO as a *t* score − 2.5 SD at the femoral neck, total hip, or lumbar spine.

Prevalent subclinical VF severity was graded according to the classification of Genant, i.e., grade I (mild) 20%–< 25%, grade II (moderate) 25%–< 40%, and grade III (severe) > 40% height loss [30].

P-EU (Bindex®)

P-EU (Bindex®; Bone Index Finland, Kuopio, Finland) was used for this study [20–22]. Cortical thickness (CTh) was calculated by multiplying the time of flight between the ultrasound echoes from the periosteal and endosteal surfaces by the speed of sound (SOS) [31]. According to manufacturers' recommendation, CTh is measured at one-third of the proximal tibia, meaning a third of the distance from the knee joint space to the medial malleolus. First, the participant was asked to bend the knee in order to palpate the knee joint. The leg was returned to a flat position while keeping contact with the medial knee joint gap. The joint was marked using a ball pen. Then the ruler was held next to the lower leg with the lower end at the most distal side of the medial malleolus. We used a manufacturer's ruler to indicate the measurement at exactly one-third of the tibia length. Echo gel was applied at this site, and the transducer was moved over the tibia at a slight angle. This movement was repeated five times to obtain five valid signals.

All measurements were performed by the same operating technician who was trained by the manufacturer. These 5 results were averaged, computed further in the software (Bindex® software v2.0) using CTh, age, weight, and height. Density index (DI, g/cm^2) was calculated with Bindex® software [20–22]. After 2 days of training the local operating technician by the manufacturer, the inter-rater agreement between the manufacturer's instructor and the local operator was tested (inter-rater reliability (IRR) was 87%; $R^2 = 0.8716$, CV = 3.2%) measuring 16 patients, which reflects a high agreement [32].

Aims of the study

We studied various P-EU cut-off levels to determine the proportion of women with a true negative P-EU test for having no osteoporosis at the femoral neck, total hip, or lumbar spine, and/or a subclinical VF with the consequent proportion of women with a false negative P-UE test, i.e., the confirmed presence of osteoporosis or at least one subclinical prevalent VF according to DXA/VFA. The first step in this research was to study the manufacturer's recommended P-EU (Bindex) DI score of 0.844 g/cm^2 that was originally developed and tested for osteoporosis at the hip and femoral neck.

The second step was to determine the P-EU DI threshold with the highest proportion of true negative tests at the expense of the lowest proportion of false negative tests.

Statistical methods

Statistical analyses were performed using StatGraphics Centurion software (version 17.2.05 for MS-Windows; Statpoint, Inc., Warrenton, VA, USA) and R (2018, The R Foundation for Statistical Computing Platform, version 3.5) [33]. All DXA and VFA scores were dichotomized being Yes = 1 (*t* score − 2.5 SD and/or at least one prevalent VF 25%) and No = 0 (*t* score > − 2.5 SD and no prevalent VF 25%).

The Wilcoxon-Mann-Whitney rank-sum test was used to compare two groups formed by censoring via DXA spine, total hip, and femoral neck (osteoporosis and osteopenia/normal) and dichotomized DI as the outcome variable. The Kruskal-Wallis test was used to compare these groups among the various numerical variables DI and DXA spine, DXA total hip, and femoral neck *t* scores. Pearson's chi-square test or Fisher's exact probability test was used to examine the significance of the association between dichotomized DI and dichotomized DXA total hip, DXA femoral neck, DXA lumbar spine, DI *t* scores, and Genant classifications. OR and 95% CI were calculated to assess the effect size of a significant association. The diagnostic accuracies of varying DI threshold levels to predict *t* score defined osteoporosis and/or subclinical VF grade II and III were analyzed performing ROC analyses aiming to find DI threshold values corresponding with AUC > 80%.

Spearman's rank correlations were calculated between DXA lumbar spine, femoral neck, and total hip; DI *t* scores; and Genant classification vs. numerical DI as outcome variable before establishing the most adequate logistic regression model, as well as for the interpretation of the inter-rater reliability. Collinearity and interactions were analyzed using R and judged by interpretation of VIF, condition indices, and interaction trees and plots. Receiver operator curve (ROC) analyses were performed using library pROC in R aiming to achieve an area under the ROC curve (AUC = auroc) > 80% [34].

The best DI threshold (method Youden), all other thresholds, and adhering diagnostics like sensitivity, specificity, NPV, PPV, and their respective 95% CI were calculated by bootstrapping using typically 10,000 replicates to obtain good estimates of statistics and adequate significant figures [35].

For the calculation of the proportion of correctly and incorrectly non-referred women for DXA/VFA, we calculated by

tabulation the number of women who are above or below a specific threshold DI (g/cm^2) and had a dichotomous score in DXAVFAALL and related that number to *N* (the total number of women).

p value < .05 was considered statistically significant at the 95% confidence level.

Results

Of a total of 591 consecutive women with a NVF, we excluded 122 women with finger, toe, and skull fractures (Fig. 1). Therefore, 469 patients were invited at the FLS resulting in 263 attenders (56%) and 206 FLS non-attenders (44%). After the exclusion of 54 women (18 with a clinical VF, 9 no informed consent, 20 with unreadable or incomplete data, 7 not accessible for P-UE measurement), the study population consisted of 209 women.

Patient characteristics are provided in Table 1. Median age was 62.2 ± 6.0 years; 19 women (9%) had a hip fracture, 94 (45%) a non-vertebral/non-hip major fracture, and 96 (46%) a non-vertebral/non-hip minor fracture. Osteoporosis was present in 83 women (40%) and/or at least one prevalent subclinical VF was present in 10 women while 7 women had a VF without osteoporosis. Seventy-three women (35%) had osteoporosis but no prevalent subclinical VFs.

Applying the manufacturer's standard P-EU threshold (DI 0.844 g/cm^2) resulted in 130 women with a DI ≤ 0.844 g/cm^2 (62%) and 79 with women with a DI > 0.844 (38%).

Odds ratios of a DI 0.844 g/cm^2 for not having osteoporosis at the femoral neck, total hip, or lumbar spine, and for not having osteoporosis or subclinical VFs, respectively, are presented in Table 2.

The diagnostic accuracy of DI thresholds for any combined DXA/VFA outcome according to the ROC analyses are presented in Table 3. The ROC diagnostic accuracy analysis of P-EU (Bindex®) is depicted in Fig. 2.

Table 4 shows the number and proportion of true negative and false negative tests for a range of DI thresholds including that formulated by the manufacturer (from 0.844 to 0.896 g/cm^2). Use of the manufacturer's recommended DI cut-off of ≥ 0.844 g/cm^2 resulted in 77/209 true negative (37.8%) and 12 (5.8%) false negative tests. The lowest proportion of false negative tests was achieved at a DI of 0.896 g/cm^2 being true negative in 38 women (18.3%) and false negative in 2 women (1%) in whom one with a subclinical VF and one woman with osteoporosis but no subclinical VF.

Discussion

In this cross-sectional pilot study, we showed the outcome results of several P-UE DI thresholds (including the cut-off DI of 0.844 g/cm^2) as recommended by the manufacturer. The proportions of true negative and false negative tests were calculated to get the first notion about potential DXA/VFA non-referrals because of no suspicion of osteoporosis and/or a subclinical vertebral fracture on VFA in parallel with proportions

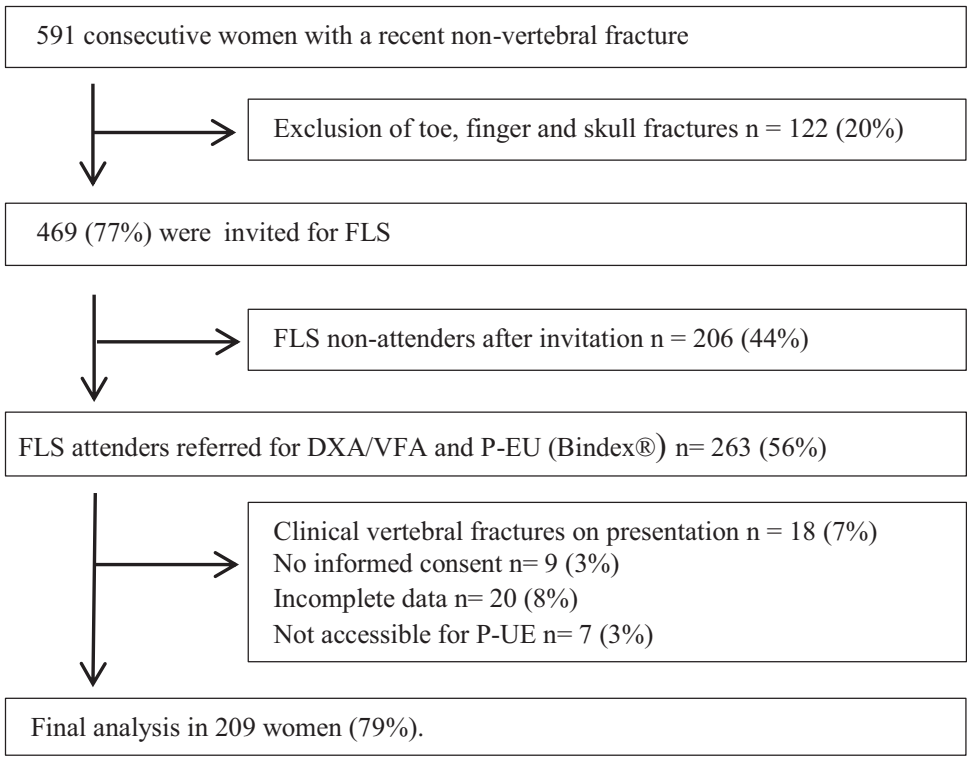

Fig. 1 Flowchart of the current study

Table 1 Characteristics of 209 women, 50–70 years old, with a recent non-vertebral fracture at the FLS

	Number (%)	Median	Range (min/max)	
Age (years)	209 (100%)	62.2	50	70
Osteoporosis	83 (40%)			
Osteopenia	92 (44%)			
Norma BMD	34 (16%)			
At least one prevalent VF (Genant grade II/III)				
Grade II (25% but 40%)	13 (6%)			
Grade III (> 40%)	4 (2%)			
Hip fracture*	19 (9%)			
Major fractures* $n = 94$ (45%)				
Distal radius and lower arm	52 (55%)			
Sub-capital humerus	16 (17%)			
Rib	6 (6%)			
Pelvis and acetabulum	6 (6%)			
Tibia proximal/plateau	10 (11%)			
Calcaneal/tarsal	10 (11%)			
Minor fractures* $n = 96$ (46%)				
Clavicle/scapula	6 (6%)			
Scaphoid	7 (7%)			
Metacarpal	12 (13%)			
Radius neck/head	9 (9%)			
Patella	7 (7%)			
Ankle/malleolus	25 (26%)			
Metatarsal	18 (19%)			
Age at menopause (self-reported; years)		50	41	61
DXA femoral neck *t* score (SD)		− 1.9	− 4.4	+ 1.3
DXA total hip *t* score (SD)		− 1.6	− 5.2	+ 2.4
DXA *t* score lumbar spine (SD)		− 1.6	− 5.2	+ 2.4
Cortical thickness (CTh) (mm)		2.1	1	2.3
Density index (DI) (g/cm^2)		0.82	0.667	1.183
Density index *t* score (SD)		− 1.6	− 3.4	+ 2.7
BMI (kg/cm*cm)		21.8	16.1	23.1
Weight (kg)		68	45	130
Height (cm)		168	149	188
Smoking (yes)	44 (19%)			
Alcohol (> 2 U/daily)	33 (15%)			
Previous fracture(s): yes (self-reported)	53 (23%)			
Previous fall: yes (self-reported)	23 (10%)			
Parental hip fracture (mother: yes)	23 (10%)			
Parental hip fracture (father: yes)	9 (4%)			
Rheumatoid arthritis (existing)	11 (5%)			
Diabetes (existing)	9 (4%)			
Hyperthyroidism (existing)	2 (1%)			
COPD	16 (7%)			
Vitamin D supplementation (yes) (Nr. conc. nmol/l)	105 (46%)	68	18	175

*Fractures were categorized according to Warriner [29]

of false negative results down to 1%. The results are relevant since there are no previous studies performed in high-risk FLS patients that focussed on screening with peripheral ultrasound technology showing an 18.3% proportion of true negative tests (indeed no osteoporosis and/or prevalent subclinical VFs grade II/III).

Table 2 Odds ratio's (OR) using the manufacturer's density index (DI) 0.844 g/cm^2 to exclude for osteoporosis and/or subclinical vertebral fractures in 209 women who sustained a recent non-vertebral fracture

DXA per site	*p* value	95% CI	OR
DXA femoral neck	< .001	7.46, 61.76	21.47
DXA total hip	< .001	3.43, 38.31	11.47
DXA spine	< .001	3.69, 25.14	9.68
DXA ALL sites	< .001	2.69, 10.23	5.25
DXA ALL sites (including subclinical vertebral fractures grades II and III)	< .001	2.54, 9.61	4.94

DI measures (g/cm^2) in women with and without osteoporosis (dichotomized DI 0.844: 0 and 1 resp.). DXA measures were dichotomized for osteoporosis (*t* score − 2.5 SD: 1) at least at one of the DXA sites (femoral neck, total hip, and spine) and/or grades II and III prevalent vertebral fractures. *OR*, odds ratio; *95% CI*, 95% confidence interval. *p* value < .05 is considered significant

Previous studies were limited in reporting the accuracy of peripheral ultrasound devices with a more general approach to find optimal cut-off thresholds for "osteoporosis" based on central DXA, but not to additionally diagnose those patients with a subclinical VF. In this context, it has been shown that the diagnostic inaccuracy of ultrasound techniques mostly using ROCs ranged from 0 to 12.4% with DXA savings from 3 up to 69% [16–18, 20, 21].

In this study, Bindex® showed a good diagnostic accuracy for DXA-defined femoral neck osteoporosis (AUC > 0.81) and a fair accuracy for DXA measurements at the lumbar spine and total hip and for the combination of the three locations and subclinical VFs ≥ 25% (Tables 2 and 3; Fig. 2).

ROC analysis comparing P-UE versus DXA/VFA outcomes showed an optimal AUC of 78.4% at a DI of 0.837 g/cm^2, which is almost equivalent to manufacturers' recommended DI of 0.844 g/cm^2. However, the aim of the study was not to test the accuracy of P-UE but to identify a specific DI threshold that covers optimal balance between true negative and false negative test results as compared with the results generated by DXA/VFA. The lowest DI threshold reported here was the manufacturers' recommended DI of 0.844 g/cm^2 followed by a range of higher DI cut-off steps up to 0.896 g/cm^2. Using the composite DXA at all sites/VFA measure (DXAVFAALL; see Table 3), a calculated range of true negative and false negative results is shown in Table 4. In this single-center FLS cross-sectional study and according to the current definition, we found true and false negative test outcomes to be optimally balanced at a DI cut-off of 0.896 g/cm^2. By doing so, we found 18.3% true negative and 1% false negative P-UE tests. This higher DI as compared with recommendation enables safely the identification of a substantial proportion of women who may be in no need for DXA/VFA referral. However, prospective studies are further needed. This pilot study was performed in a small FLS group of women among 50 to 70 years of age, assuming that the prevalence of subclinical VFs was not very high in this group of women and that it therefore could be of additional value to perform screening with a peripheral device in this group of women. By doing so, the prevalence of osteoporosis was 40% and of one or more subclinical VFs 8%, which is similar to previous Dutch studies and also to a UK cohort [15, 24, 36].

It is of note that the attendance rate in most FLSs is only around 50% of all patients with a fracture regardless of face-to-face patient information and of FLS invitations by letter afterwards [8, 36]. Besides the fact that 18.3% of women had a true negative test based on DI of 0.896 g/cm^2 and may be confidently not in need of DXA/VFA, there may be another advantageous aspect of immediate post-fracture screening with a mobile device. A "positive" Bindex test could promote

Table 3 Calculated Bindex density index (DI) cut-off for achieving the optimal AUCs according to DXA with or without subclinical grades II and III on VFA, using ROC analyses

DXA sites	DXAVFAALL including VF grade II/III	DXA ALL sites	DXA lumbar spine (L1–4)	DXA femoral neck	DXA total hip
Optimal DI cut-off	0.837	0.837	0.822	0.812	0.837
AUC (= auroc)	0.7844	0.7878	0.7337	0.7841	0.8116
Specificity (%)	60.2	60.0	59.4	63.5	59.9
Sensitivity (%)	87.2	88.1	81.5	78.6	92.5
NPV (%)	87.1	88.2	90.2	92.2	93.6
PPV (%)	60.5	59.7	41.1	35.1	55.6

Optimal DI cut-offs (numerical, g/cm^2) are obtained from the receiver operator curve (ROC) analyses. The calculated optimal DI cut-off agreed with that of the manufacturer's recommended cut-off. *Auroc*, area under the receiver operator curve; *NPV*, negative predictive value; *PPV*, positive predictive value

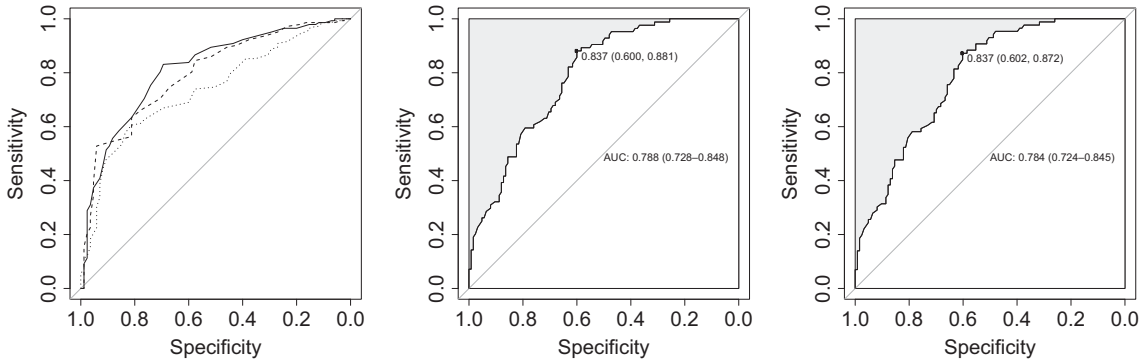

Fig. 2 ROC curves. **a** Three DXA-based predictors vs. dichotomized Bindex® density index predictors. **b** Density index (numerical) vs. dichotomized DXA ALL sites. **c** Density index (numerical) vs. dichotomized DXAVFAALL sites including all subclinical vertebral fractures grades II and III. The area under each ROC curve (i.e., auroc) quantifies the overall ability of each "diagnostic test" to discriminate between women (50–70 years) with suspicion of osteoporosis (dichotomized DI ≤ 0.844) and those without osteoporosis (dichotomized DI > 0.844). From the three curves, in **a**. it can be seen that the 3 predictors may be able to discriminate between the two groups of women. The 95% confidence intervals of the aurocs are not significantly different between femoral neck (auroc, 0.8116; 95% CI, 0.7506–0.8726) and total hip (auroc, 0.7841; 95% CI, 0.7209–0.8473) and between total hip and lumbar spine (auroc, 0.7337; 95% CI, 0.6656–0.8017). However, aurocs of the femoral neck and lumbar spine are significantly different (bootstrap method; *p* value .02). The area under the ROC curve (i.e., auroc) quantifies the overall ability of the "diagnostic test" DI to discriminate between women (50–70 years) with and without osteoporosis and clinical vertebral fractures with DXAVFA ALL site–based absence of osteoporosis (**c.**) with and without vertebral fractures grades II and III. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold of the respective predictor

Table 4 Proportion of true positive and false negative tests in women 50–70 years for not having osteoporosis and/or prevalent morphometric vertebral fractures according to different density index (DI) cut-offs

True negative and false negative tests					Test characteristics			
Measured DI	True negative (nr.)	True negative (%)	False negative (nr.)	False negative (%)	NPV (%)	PPV (%)	Specificity (%)	Sensitivity (%)
0.844	65	31.3	12	5.8	84.40	58.80	54.60	86.50
0.846	65	31.3	11	5.3	85.50	59.10	54.60	87.60
0.848	63	30.3	11	5.3	85.10	58.20	52.90	87.60
0.851	60	28.8	11	5.3	84.50	56.90	50.40	87.60
0.854	60	28.8	10	4.8	85.70	57.20	50.40	88.80
0.855	59	28.4	9	4.3	86.80	57.10	49.60	89.90
0.857	58	27.9	9	4.3	86.60	56.70	48.70	89.90
0.860	57	27.4	9	4.3	86.40	56.30	47.90	89.90
0.862	57	27.4	8	3.8	87.70	56.60	47.90	91.00
0.864	56	26.9	7	3.4	88.90	56.60	47.10	92.10
0.866	54	26.0	7	3.4	88.50	55.80	45.40	92.10
0.868	52	25.0	7	3.4	88.10	55.00	43.70	92.10
0.870	51	24.5	7	3.4	87.90	54.70	42.90	92.10
0.872	49	23.6	7	3.4	87.50	53.90	41.20	92.10
0.875	47	22.6	7	3.4	87.00	53.20	39.50	92.10
0.876	46	22.1	7	3.4	86.80	52.90	38.70	92.10
0.879	45	21.6	6	2.9	88.20	52.90	37.80	93.30
0.881	44	21.2	6	2.9	88.00	52.50	37.00	93.30
0.883	43	20.7	5	2.4	89.60	52.50	36.10	94.40
0.884	41	19.7	5	2.4	89.10	51.90	34.50	94.40
0.886	41	19.7	3	1.4	93.20	52.40	34.50	96.60
0.890	40	19.2	3	1.4	93.00	52.10	33.60	96.60
0.893	39	18.8	3	1.4	92.90	51.80	32.80	96.60
0.895	38	18.3	3	1.4	92.70	51.50	31.90	96.60
0.896	38	18.3	2	1.0	95.00	51.80	31.90	97.80

True negative and false negative tests in women 50–70 years not having osteoporosis and/or grade II or III vertebral fractures by application of various (higher) DI cut-offs. DI cut-offs are obtained from receiver operator curve (ROC) analyses in DXAVFAALL. *NPV*, negative predictive value; *PPV*, positive predictive value

the awareness for having a condition in order to motivate them for further assessment at the FLS. In fact, of the women with a DI ≤ 0.896 g/cm^2, 50% had osteoporosis and/or a VF. Screening may, therefore, be promising to encourage a proportion of individuals to attend the FLS, who would have decided otherwise not to attend the FLS [8]. This easy to operate hand-held non-ionizing tool offers an important opportunity as it can be used during the early stages of fracture care, being the optimum moment when the patient realizes that there might be a problem with skeletal health.

This study has several limitations. First, it was conducted in a small group of women of 50–70 years and not among older women and men. FLS attendance was again confirmed to be low. Therefore, the results can not be extrapolated to elderly women or men. Second, the percentage of osteoporosis was higher than expected. Third, the number of subclinical VFs was smaller than expected; the prevalence of grades II and III VFs increases with age [24, 25]. This low number found may be a confounder in the interpretation of the results. However, the higher the prevalence of patients with osteoporosis or subclinical VFs, the lower will be the proportion of subjects that is correctly excluded for DXA/VFA referral. Secondly, data were obtained from FLS attenders and not from FLS non-attenders. FLS attenders who were requested to consent with a scientific study are probably different from FLS non-attenders [36]. Since this study was post-hoc analyzed, this discrepancy may have caused selection bias. Therefore, further studies in a complete consecutive cohort of patients of 50 years and older including men with a recent fracture are needed. In addition, whether the screening approach would result in higher FLS attendance has to be further studied. Finally, this is a single-center FLS study; comparisons with and experiences from other FLS centers are still needed.

In conclusion, based on specific P-EU thresholds, a substantial proportion of women between 50 and 70 years with a recent NVF could confidently not be referred for further assessment with DXA/VFA. Moreover, the strategy of immediate screening during post-fracture care may help to improve FLS attendance and DXA/VFA testing in patients with a positive screening outcome.

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Compliance with ethical standards

Conflict of interest None.

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