



# Pulse-echo ultrasound measurement in osteoporosis screening: a pilot study in older patients

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## Abstract

**Background** A mere 25% of patients who need treatment for osteoporosis receive appropriate therapy, partly due to the time-consuming and stressful diagnostic workup for older patients with functional decline.

**Aims** The purpose of the present study was to investigate the accuracy of pulse-echo ultrasound measurement of the lower leg for the detection of osteoporosis in older patients, and evaluate the effect of a proposed diagnostic algorithm.

**Methods** Cortical thickness and the so-called density index (DI) were measured prospectively on the lower leg with a pulse-echo ultrasound (PEUS) device. The accuracy of the device was compared with dual-energy X-ray absorptiometry (DXA) of the hip. We calculated algorithms combining FRAX® scores and PEUS measures as a guide for specific treatment of osteoporosis.

**Results** Three hundred and thirty-three patients aged on average 81 years (82.1% women, 275/333) were included in the study. The sensitivity of the ultrasound device versus DXA for the detection of osteoporosis was 94.4% (84/89), and the specificity was 59% (144/247). The gender-specific sensitivity was 96.2% (75/78) for women and 81.8% (9/11) for men.

**Discussion** Clinical decisions for the specific treatment of osteoporosis could be based on the proposed algorithm, without additional DXA measurements, in 90.9% (303/333) of the patients.

**Conclusion** Older patients with a similar risk profile as in our study population may benefit from PEUS, as it is a non-invasive, cost-effective, and efficient diagnostic tool with high accuracy in screening patients for osteoporosis and the risk of fractures.

**Keywords** Pulse-echo ultrasound · Osteoporosis · Fracture risk · Accuracy · Bone mineral density

## Introduction

One third of all women and one sixth of all men experience an osteoporotic fracture during their lives [1]. Fractures at the hip, spine, forearm, and humerus, associated with low bone mineral density, are interpreted as osteoporotic

fractures [2]. Bone metabolism in elderly persons differs from that in younger adults [3]. Studies focused on osteoporosis in men are fewer than those in women [4, 5]. Although the rate of fragility fractures in men is just about a third of that in women, a rising prevalence has been predicted in Western countries [6, 7]. The higher fracture rate in women is attributed to the smaller diameter of bone, specific bone architecture, higher bone resorption with advancing age, and a higher risk of falls [8, 9].

According to current clinical practice, the diagnosis of osteoporosis is based on a low bone mineral density (BMD) quantified with dual-energy X-ray absorptiometry (DXA) [10]. Providing a more convenient diagnostic workup for older patients with functional loss, we need point-of-care screening tests for osteoporosis and/or fractures [11–13]. Many fragility fractures occur in patients with normal bone density values or osteopenia on DXA, which highlights the need for appropriate detection of fracture risk [14]. It has been reported that only 25% of patients who need treatment

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received it in an appropriate manner [15]. Even after a fragility fracture, a mere 21.4% were diagnosed with osteoporosis [16].

Importantly, the diagnostic value of DXA is reduced by the fact that it does not demonstrate the character of altered bone quality [8, 17]. Simpler and more easily accessible devices for osteoporosis screening are being investigated [18–20]. A negative association was noted between pulse-echo ultrasound measurement (PEUS) of cortical thickness (CT) at the lower leg and osteoporosis [21, 22]. The PEUS is a portable pulse-echo device employing a 3.0 MHz ultrasound frequency, connected to any laptop via a USB port [23]. In line with the recommendations of the International Society for Clinical Densitometry, the accuracy of new devices for the detection of osteoporotic BMD should achieve a sensitivity of 90% and a specificity of 90% as compared to DXA [24]. Published data for Finnish patients at five private health care centers and one public university demonstrated the high accuracy of PEUS. However, the sensitivity (84.7%) and specificity (82.0%) failed to achieve the recommended accuracy [25]. A high rate of aptness was also noted in a group of Hispanic and Caucasian women [26]. Both studies included women aged 61 to 68 years.

Based on an algorithm proposed in 2008, the World Health Organization developed a fracture risk assessment tool named FRAX® to determine the risk of fracture in men and women, and created a Web-based program for different countries [27]. Using the FRAX® score as a screening tool and classifying patients into those with a high, intermediate, and low risk of fractures based on PEUS measurements may be used to suggest treatment alternatives for osteoporosis and, thus, reduce the need for subsequent DXA measurement, as proposed by Karjalainen [28, 29]. Using this algorithm in 448 Caucasian women aged on average 68 years, it was found that only 16% needed further DXA measurement [26]. This diagnostic pathway is cost effective, as shown in a study performed by Soini in postmenopausal Finnish women [30].

To investigate the accuracy of PEUS in elderly patients with multimorbid conditions and to evaluate the applicability of the proposed algorithm, we studied elderly women and men admitted to a Department of Acute Geriatrics with or without sustained fractures. We hypothesized that PEUS measurements compared to DXA measurements had a high accuracy for the detection of osteoporosis.

## Materials and methods

The Department of Acute Geriatrics is a specialized medical unit for geriatric patients in Upper Austria, serving a population of approximately 230,000 individuals.

## Subjects

The study coordinator (PD) reviewed all admissions to the department. We prospectively included women and men with a risk factor for osteoporosis in accordance with the guidelines [6]. We excluded patients receiving ongoing treatment for osteoporosis, those without both lower extremities, patients with an inflammatory or neoplastic bone disease, and those who were unable to provide written consent (Supplement 1). Informed consent was obtained in writing from all patients prior to enrollment. A specialist of internal medicine recorded the patients' medical history and performed a physical examination. The presence of malnutrition was determined by the Mini Nutritional Assessment. Sarcopenia was assessed by measuring gait speed, handgrip, and workup in accordance with the recommendations of the European task group for sarcopenia in the elderly, as part of a comprehensive geriatric assessment at the Department of Acute Geriatrics. The risk of falls was assessed using the Tinetti test, and functional abilities in daily living with the Barthel index. [31–33]. We performed laboratory tests, dual-energy X-ray absorptiometry, and fracture risk assessment if indicated, in accordance with the national guidelines for the treatment of osteoporosis. The study was approved by the ethics review board of Upper Austria in accordance with the Declaration of Helsinki 1964, revised in 2013 at the general assembly in Fortaleza, Brazil (ethics committee approval number 1103/2018).

## FRAX® score

The calculation of fracture risk was based on patient data including age, gender, weight, height, and several validated risk factors (prior fragility fracture, parental history of hip fracture, current smoking habits, current use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol consumption). These data were collected without measuring BMD to assess the accuracy of the proposed diagnostic option without the use of DXA. The likelihood of fractures differs significantly in the various countries [1]. Therefore, FRAX® scores were calibrated to the known epidemiologic data for fracture risk in Austria. The age-stratified intervention threshold and BMD assessment thresholds were based on tables and diagrams proposed by Kanis JA et al. [34].

## Bone mineral density

Bone mineral density (BMD) was measured at the femoral neck using the Lunar Prodigy densitometer (General Electric Company, Madison, WI, USA) at the Department

of Radiology in the Hospital of Gmunden. Quality control was performed daily using a specific software. Both hips were scanned (except in cases of joint replacement or osteosynthesis material from previous surgery), and the lowest T-scores were used for the study. Based on the WHO definition, a T-score  $\leq -2.5$  was interpreted as osteoporosis [10].

### Pulse-echo ultrasound measurements (PEUS)

The mobile Bindex® device (Bone Index Finland, Kuopio, Finland) was used for PEUS measurements. This point-of-care instrument was connected to a Universal Serial Bus port of a personal computer. An electrical pulse was transmitted into 3.0 MHz ultrasound waves that were sent through the skin to the proximal tibia. The standardized site of measurement was at a third of the length from the proximal head of the tibia to the medial malleolus, using anatomical landmarks and a manufacturer's ruler. Ultrasound gel was applied, and the transducer was moved over the tibia at a slight angle. This maneuver was repeated five times, and the mean was determined. The same study staff performed the measurements for each patient (AR); the operator had no information on the values of DXA measurement. Cortical thickness was determined by multiplying the time lag between the ultrasound echoes from the periosteal to the endosteal surfaces, and was analyzed by the software of the device [21]. Cortical thickness, combined with data regarding the patient's age, weight, and height were used to calculate the density index (DI), which was an estimation of BMD [23].

### Statistical analysis

For the power calculation, we anticipated a dropout rate of 10%. The probability of a type-I-error was set to 0.05. A minimum of 335 patients had to be recruited to determine a power of effect of 0.8. SPSS software (version 25.0; SPSS Inc., Chicago, IL) was used for all statistical analyses. A descriptive analysis was performed to classify patients into those with or without fractures. Pearson's correlation analysis was applied for normally distributed parameters. The Shapiro–Wilk test and visual evaluation of histograms were used to evaluate the normality of distributions, and Levene's test was applied for the evaluation of homogeneity of variances. Student's *t* test was used to compare normally distributed parameters between subjects. The level of significance was set to  $p \leq 0.05$ . Separate analyses were performed for patients with and without fractures, as well as for men and women. Categories of DI at the upper, lower, and intermediate thresholds for the diagnosis of osteoporosis were based on the publication of Karjalainen et al. 2018 [25]. In accordance with the thresholds, 90% of the patients without osteoporosis were estimated over the threshold of the lower

value and 90% of patients with osteoporosis were estimated below the upper value of DI measurements. In accordance with the published algorithm, patients with values between these thresholds had to be investigated further to establish the diagnosis of osteoporosis.

All DXA measurements were dichotomized according to the threshold of  $-2.5$  SD. We used the thresholds for osteoporosis published by Karjalainen to classify DI measurements (upper 0.844, lower 0.779) [28]. Sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated to assess PEUS in the detection of osteoporosis. Receiver operating characteristic (ROC) curves were plotted to compare the diagnostic accuracy of DI measurements with DXA measurements; true positive rates (TPR) were plotted against false positive rates (FPR) for both methods. Statistical interpretation of the estimated area under the curve (AUC) was additionally used to classify osteoporosis by the ultrasound method. We employed the Eta statistic to determine the strength of association between nominal and interval variables, and the analysis of variances to test for differences or correlations in the effects. The Youden index was used to calculate the thresholds for DI for women, men, age groups, and fracture status [35].

### Results

From September 2018 to July 2021, 3448 patients were admitted to the Department of Acute Geriatrics. Based on the inclusion criteria, we recruited 335 patients for the study. Due to the large number of patients with functional and/or cognitive decline (Table 1), only 9.7% of the admitted patients could be approached to participate in the study. Two patients were lost to analysis due to missing values. No patient refused to undergo the PEUS investigation. The patients were aged on average 81 years; 82.1% (275/333) were women, which was equivalent to the age-adjusted sex distribution in the Austrian population. The high rate of stage II–IV renal failure (73%, 244/333) and the large number of previous incurred fractures (59.1%, 196/333) reflected the high rate of comorbidity in patients admitted to the department. These patients had a higher mean age and a higher body mass index than those without fractures. There were no differences between groups with respect to gender, smoking habits, or comorbidity rates. Based on published thresholds for DXA measurements, we registered 89 patients (26.7%, 89/333) with osteoporosis and a higher rate of osteoporosis in patients with sustained fractures (37.2%, 73/196) versus those without fractures (11.7%, 16/137) (Table 1). The correlation of bone density parameters measured with DXA and PEUS showed a medium strength of association, indicating a moderate predictive value for fracture risk using either method for the measurement of BMD (Table 2).

**Table 1** Patient characteristics ( $n = 333$ )

Variable	Total	With previous fractures (n = 196)	Without previous fractures (n = 137)	<i>p</i> value
Age at enrollment, years ( $\pm$ SD)	81 (5,6)	81.5 (5.7)	79.8 (5.3)	0.003
Female (%)	275 (82.1)	164 (83.7)	111 (81)	0.266
Osteoporosis*(%)	89 (26.7)	73 (37.2)	16 (11.7)	<0.001
Osteopenia*(%)	182 (54.6)	103 (52.6)	79 (57.7)	0.179
Body mass index, kg/m <sup>2</sup> ( $\pm$ SD)	25.2 (4.6)	25.1 (4.3)	27.1 (4.9)	<0.001
Smoking (self-reported)	24 (0.7)	15 (7.7)	9 (6.6)	0.262
Diabetes	69 (20.7)	36 (18.4)	33 (24.1)	0.103
Hyperthyroidism	21 (6.3)	13 (6.6)	8 (5.9)	0.392
COPD (GOLD stadium $\geq$ 2)	28 (8.4)	17 (8.7)	11 (8)	0.418
Hemoglobin, g/l	11.1 (1,7)	11 (1.7)	11.3 (1.8)	0.074
eGFR, ml/min ( $\pm$ SD)	73.8 (25.5)	75.4 (25.9)	71.5 (24.8)	0.09
PTH, pg/ml ( $\pm$ SD)	51.8 (34.6)	49.5 (27.4)	55.1 (42.6)	0.188
Previous fractures**		196 (59)	137 (41)	
Hip		105 (31.5)		
Pelvis		27 (8.1)		
Spine		17 (5.1)		
Humerus		15 (4.5)		
Lower leg		11 (3.3)		
Rips		11 (3.3)		
Forearm		10 (3)		
Other fractures		5 (1.5)		
Vitamin-D deficiency***	236 (70.9)	135 (68.5)	101 (74.3)	0.413
FRAX® score risk in %				
Without BMD measurements, risk for hip fractures ( $\pm$ SD)	13 (7.7)	18 (7.4)	8.6 (5.6)	<0.001
Without BMD measurements, risk for major fractures ( $\pm$ SD)	27 (10.8)	35 (9.5)	19 (7.9)	<0.001
DXA lumbar spine T-score ( $\pm$ SD)	-0,6 (1.9)	-0.8 (1.8)	0.2 (1.9)	<0.001
DXA total hip T-score ( $\pm$ SD)	-1,9 (1.1)	-2 (1.3)	-1.2 (1.3)	<0.001
Cortical thickness, mm ( $\pm$ SD)	1,8 (0.9)	2 (0.9)	2.1 (0.1)	0.151
Density index, g/cm <sup>3</sup> ( $\pm$ SD)	0,78 (0.1)	0.77 (0.1)	0,8 (0.1)	0.007
Appendicular skeletal muscle mass index; kg/m <sup>2</sup> ( $\pm$ SD)	6.2 (1.1)	6.2 (1.1)	6.3 (1.2)	0.098
Malnutrition (MNA 0–11/14)	87 (26.1)	51 (26)	36 (26.5)	0.513
Sarcopenia in women §	80 (23.9)	52 (26.5)	28 (20.4)	0.247
Sarcopenia in men §	31 (9.4)	16 (8.2)	15 (10.9)	0.567
Barthel index ( $\pm$ SD)	85 (15)	80 (16.1)	85.1 (14.1)	<0.001
Tinetti test ( $\pm$ SD)	19 (5.2)	18 (5.2)	19.6 (4.8)	<0.001
Handgrip ( $\pm$ SD)	18 (7.3)	16.8 (7.3)	19.1 (7.3)	0.082
Gait speed, m/second ( $\pm$ SD)	0.53 (0.1)	0.5 (0.2)	0,6 (0.2)	<0.001

Note: *SD* standard deviation, *GOLD* Global Initiative For Chronic Obstructive Lung Disease (severity grade of chronic obstructive lung disease), *eGFR* estimated glomerular filtration rate according to MDRD study equation, *PTH* parathyroid hormone, *BMD* bone mineral density, *DXA* dual-energy X-ray absorptiometry, *MNA* mini nutritional assessment test (Vellas B, Guigoz Y, Garry PJ, Albaredo JL. The Mini Nutritional Assessment. Paris: Serdi Publishing Company. 1994; \*Osteoporosis and osteopenia were diagnosed in accordance with the guideline of Kanis et al.2021; \*\*Fractures of toes, fingers, skull and patella were excluded, also multiple fractures were counted; \*\*\*diagnosed in accordance with De Pascale G et al. 2014; §, sarcopenia was defined on the revised European consensus on definition and diagnosis by Cruz-Jentoft et al. 2019; §§, categories of Density index were built on the publication of Karjalainen et al. 2018

The overall sensitivity of PEUS was 94.4% (84/89). Gender-specific sensitivities were 96.2% (75/78) for women and 81.8% (9/11) for men. Large differences were noted between patients with sustained fractures (98.5% or 64/65 of women,

versus 87.5% or 7/8 of men) and those without fractures (78.6% or 11/14 of women, versus 66.6% or 2/3 of men), which reflects a gender difference in the accuracy of DI measurements. The opposite was observed with respect to

**Table 2** Correlations of pulse-echo ultrasound measurements and DXA measurements

	DI, g/cm <sup>3</sup>	CT, mm
DI, g/cm <sup>3</sup>	1	0.887 (<0.001)
CT, mm	0.887 (<0.001)	1
BMD-spine, g/cm <sup>3</sup>	0.371 (<0.001)	0.228 (<0.001)
BMD-hip (g/cm <sup>3</sup> )	0.461 (<0.001)	0.262 (<0.001)

Note: *p* value in brackets, DXA dual-energy X-ray absorptiometry, BMD bone mineral density, DI density index, CT cortical thickness

specificity, which was 89.6% for men (75/78) and 50.7% for women (101/199). Specificity was higher in men who had experienced fractures (88% 22/25) versus women who had sustained fractures (49.5%, 49/99) (Table 3).

In line with proposed algorithms of the National Osteoporosis Guideline Group for the diagnosis of osteoporosis by FRAX® scoring and the published age-specific threshold values, we developed algorithms for osteoporosis screening by combining FRAX® scoring and measurement of the density index with pulse-echo ultrasound, stratified for age and fracture status [34]. Decisions with respect to specific medical treatment for osteoporosis (osteoblastic or antiresorptive medication) or lifestyle measures could be derived from this algorithm for 90.9% (303/333) of patients; only 9.1% (30/333) needed additional DXA measurement in

accordance with the diagnostic algorithm published by Karjalainen (Fig. 1). Similar values were noted for patients over the age of 80 years (9.3%; 18/193) (Figure S2). In patients without fractures, the rates in the two age cohorts were 16.8% (23/137) and 14.9% (10/67), respectively (Figure S3, S4). Using this algorithm, clinical decisions regarding specific treatment for osteoporosis could be made accurately without further investigation for 96.5% (189/196) of patients older than 70 years of age with sustained fractures (Figure S5). The same was also achieved for patients over the age of 80 years who had experienced fractures (Figure S6).

ROC curve analyses for the sensitivity of DI measurement to classify osteoporosis by pulse-echo ultrasound against 1-specificity dichotomized T-values  $\leq -2.5$  of DXA measurements are shown in Fig. 2. Patients were divided into subgroups of age and sustained fractures. Stratified by age and fracture status, we noted higher AUC values for elderly patients and those with sustained fractures. Based on these indices, we created models for the detection of osteoporosis according to the receiver operating characteristics in our study population (Table S1).

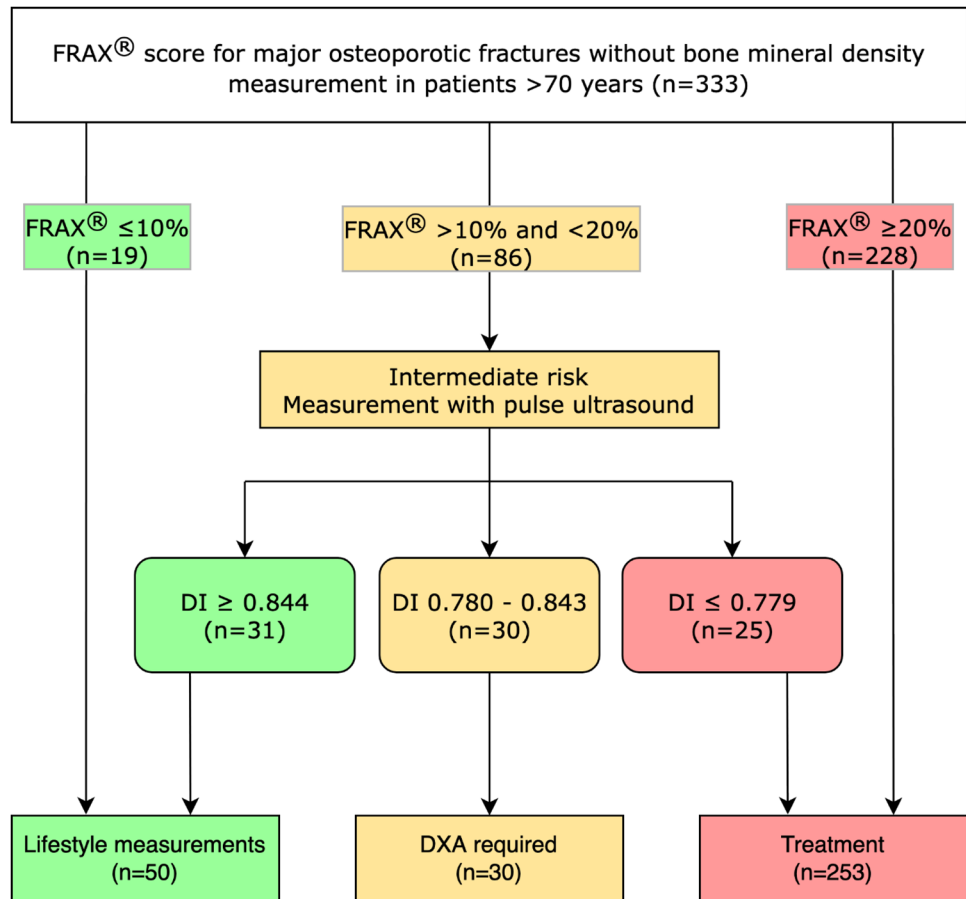
Using the ROC curve analyses, we determined cut-off values of 90% sensitivity and 90% specificity for density index measurements regarding the diagnosis of osteoporosis, splitting those values into groups based on gender, age, fracture status, and 10-year cohorts divided by the different risk levels of osteoporosis (Table S2).

**Table 3** Sensitivity, specificity, negative (NPV) and positive predictive value (PPV) of density index to identify osteoporosis measured at the hip or lumbar spine, stratified for gender and history of sustained fractures

Parameter	Without fractures ( <i>n</i> = 137)		
	Total	Women ( <i>n</i> = 111)	Men ( <i>n</i> = 26)
Sensitivity	81.2 (13/16)	78.6 (11/14)	66.6 (2/3)
Specificity	59.3 (73/123)	52 (52/100)	91.3 (21/23)
NPV	96 (73/76)	96.2 (52/54)	95.4 (21/22)
PPV	20.6 (13/63)	18.6 (11/59)	50 (2/4)
Parameter	With fractures ( <i>n</i> = 196)		
	Total	Women ( <i>n</i> = 164)	Men ( <i>n</i> = 32)
Sensitivity	97.3 (71/73)	98.5 (64/65)	87.5 (7/8)
Specificity	57.3 (71/124)	49.5 (49/99)	88 (22/25)
NPV	97.3 (71/73)	98 (49/50)	95.6 (22/23)
PPV	57.3 (71/124)	56.1 (64/114)	70 (7/10)
Parameter	Total ( <i>n</i> = 333)		
	Total	Women ( <i>n</i> = 275)	Men ( <i>n</i> = 58)
Sensitivity	94.4 (84/89)	96.2 (75/78)	81.8 (9/11)
Specificity	59 (144/247)	50.7 (101/199)	89.6 (43/48)
NPV	96.6 (144/149)	97.1 (101/104)	95.5 (43/45)
PPV	44.9 (84/187)	43.4 (75/173)	64.3 (9/14)

Note: Values are expressed as percentages (absolute values of the calculated group in brackets)

**Fig. 1** Algorithm for the diagnosis of osteoporosis using FRAX® scores and the ultrasound method in older persons



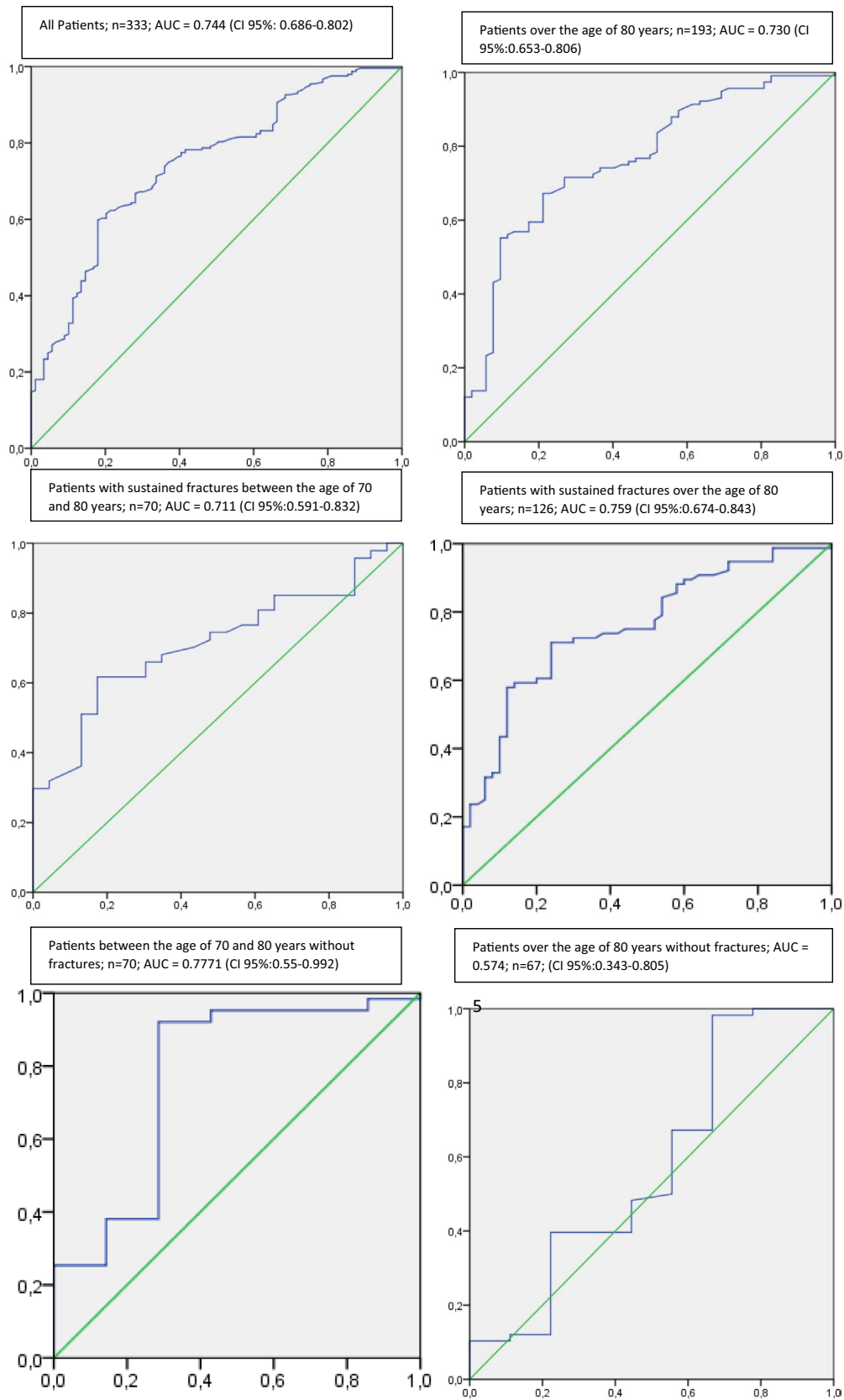
The cut-off values of the overall study group were nearly concordant with the data published by Karjalainen et al. (2018) but differed distinctly for patients older than 80 years of age. In the latter group, the upper and lower limits were lower. In men, the thresholds for the upper limit were distinctly higher.

The ROC curves plotting the dichotomized fracture status versus DXA measurement indicated an acceptable potency to classify osteoporosis (AUC 0.698; 95% CI 0.642–0.754), and a slightly weaker ability to classify based on pulse-echo ultrasound (AUC 0.606; 95% CI 0.545–0.667) (Figure S7 A). The visual impression of the ROC curves was confirmed by calculating correlations using ETA and ANOVA for fracture status and the diagnosis of osteoporosis based on pulse-echo ultrasound. ROC curves for DXA measurement of the spine were similar to those for the hip (Figure S7 B). A gender difference was seen in ROC curves for men and women in the two age groups (Fig. 3). The accuracy of diagnosis based on the algorithm, stratified for age and fracture status, was over 90% and even higher in patients with sustained fractures (Table S3).

## Discussion

Based on the algorithm presented in the study, a clinical decision with respect to specific treatment for osteoporosis could be made in 90.9% (303/333) of the elderly patients recruited for the investigation. This diagnostic approach, based on the FRAX® score and PEUS in a point-of-care setting, appears to be convenient and easily accessible for older patients. The technical requirements for the diagnostic procedure include an Internet access and a laptop with an ultrasound device. The use of this diagnostic approach has the potential to reduce the risk of further fragility fractures in patients with osteoporosis.

Since 1984, ultrasound methods have been proposed for diagnosing osteoporosis ever since the introduction of the first quantitative ultrasound methods (QUS) [36]. Several devices have been studied for the measurement of the calcaneus comparing the values of ultrasound parameters to those in young population. Poor correlation with BDM measurements by DXA was obtained and no recommendation for the diagnosis of osteoporosis could be made using



**Fig. 2** Receiver operating characteristic curves analysis (blue line) plotting the pulse-echo ultrasound measurements against dual-energy X-ray absorptiometry T-values  $\leq -2.5$ , stratified for age and fracture status. The reference line is indicated in green

this technique [37]. In 2008, Krieg MC et al. presented the official position of the International Society for Clinical Densitometry stating heel QUS proven to predict hip fractures and osteoporotic fractures in elderly women justified in situations where central DXA is unavailable [38]. However QUS-derived T-scores cannot be used for diagnostic classification of osteoporosis [26]. In a meta-analysis of Moayyeri A et al., QUS parameter was associated with fracture risk but marked heterogeneity among studies on fracture risk rising the need for further research [39].

To our knowledge, this is the first study demonstrating the feasibility of a diagnostic workup of PEUS in older patients. The poor attendance to DXA measurement is one of the reasons for deficiencies in the management of osteoporosis [13]. This is especially true of older patients with functional decline [16]. Our patients had a high degree of functional impairment, as evidenced by their low values on the Barthel index and the Tinetti score, as well as high rates of sarcopenia and malnutrition (Table 1).

The presented algorithm, based on previous data published by Karjalainen et al. (2016), provided a high diagnostic yield (90.9%; 303/333) (Figure S2-S6). It may be concluded that the PEUS device is a suitable screening tool for older patients [28]. The high correlations of PEUS with DXA render this method suitable for clinical use as a point-of-care tool for osteoporosis screening in older patients. This is in line with previous data concerning younger patients, with no multimorbidity or functional impairment [23].

The isolated use of DI measurement for the diagnosis of osteoporosis and for assessing the risk of fracture is deficient, as evidenced by its weak correlations (Table 2). The same was noted with respect to sensitivity, specificity, PPV, and NPV values. The overall sensitivity of 94.4% and the high NPV for all patients in the present study confirm the data published by Schousboe et al. 2017. Nevertheless, the specificity and PPV were lower except for men with or without sustained fractures [40].

The present investigation was the first to show different thresholds for DI measurement with PEUS for the detection of osteoporosis in men. We noted a gender difference also with respect to accuracy values for men, which may well be a result of the different anatomy and microarchitecture of the male skeleton [4].

The lower specificity registered in our study compared with the data published for Finnish patients may reflect the large number of sustained fractures among our patients, their advanced age, lifestyle differences, and perhaps genetic differences [41]. Sensitivity and specificity were lower for patients without fractures than for those with sustained fractures. Therefore, the combination of FRAX® scores and PEUS is a possible pathway to improve the diagnostic yield. Notably, we observed low AUC values in both ROC curves plotting DI values and

DXA measurements against fracture status in our patients (Figure S7 A). A similar tendency was noted for DXA values at the hip and the spine (Figure S7 B).

We saw benefits in the optional use of the presented algorithm for older patients, as it demonstrated the higher accuracy of pulse-echo ultrasound measurements for osteoporosis screening in older patients with sustained fractures (Table S1). This approach should be tested prospectively in further studies. The low AUC values for patients over the age of 80 years without sustained fractures were accompanied by a higher range of upper and lower values in the confidence intervals, because a large number of confounders and a variety of clinical conditions influenced the DI measurements in this age group (Fig. 2). The values for the presented algorithms reflect that even fewer patients require further DXA measurement compared to the data published by Karjalainen 2016 [28]. The large number of patients with sustained fractures in our study may explain this difference (Fig. 1, Figures S2-S6). The different accuracy values in patients older than 80 years of age are likely due to the waning precision of DXA measurement in the elderly, with degenerative changes in the hip and spine, their altered microarchitecture, and the higher rate of multimorbid conditions in advanced age [17, 42].

Our threshold values of 90% for the sensitivity and specificity of DI measurement using PEUS differ clearly from the data published by Karjalainen (2016) for patients in Finland (Table S2) [28]. The differences may be related to gender, fracture status, nationality, and age, and underline the need for further studies in these subgroups of patients.

## Limitations

This was a pilot study in a single center and a cohort of older patients with a high burden of comorbidities. The foremost limitations of the study are missing comparisons of diagnostic accuracy between older hospitalized patients and age-adjusted persons living at home or undergoing treatment in an outpatient setting. The effect of PEUS measurement for the prediction of fractures in a prospective setting could not be determined due to the short period of investigation but is currently being investigated by our study group. A further limitation is the small sample size of men in our study that was not primarily designed to show gender differences in the accuracy of the proposed device.

## Strengths

The study demonstrated the high sensitivity of DI measurement in screening elderly patients for osteoporosis.

## Conclusion

Older patients with a similar risk profile as in our study population may benefit from PEUS, as it is a non-invasive, cost-effective, and efficient diagnostic tool with high accuracy in screening patients for osteoporosis and the risk of fractures. PEUS measurements based on the calculated upper and lower thresholds are subject to gender differences and age-dependent accuracy values, which should be considered in the interpretation of PEUS data.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s40520-023-02404-z>.

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**Data availability** The data that support the findings of this study are available on request from the corresponding author, [PD].

## Declarations

**Conflict of interest** PD, BI, AR, GD, MW, and PP declared no financial or personal conflict of interest.

**Statement of human and animal rights** No animals were studied in our research.

**Informed consent** Informed consent was obtained in writing from all patients prior to enrollment. The study was approved by the ethics review board of Upper Austria in accordance with the Declaration of Helsinki 1964, revised in 2013 at the general assembly in Fortaleza, Brazil (ethics committee approval number 1103/2018).

**Impact statement** We certify that this work is novel. It could lead to a more convenient screening of osteoporosis in older patients and might reduce fragility fractures subsequently.

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