

Deep Learning Using High-Resolution Images of Forearm Predicts Fracture

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Abstract

Importance

Fragility fractures are a public health problem. Over 70% of women having fractures have osteopenia or normal BMD, but they remain unidentified and untreated because the definition of 'osteoporosis', a bone mineral density (BMD) T-Score $\leq -2.5SD$, is often used to signal bone fragility.

Objective

As deep learning facilitates investigation of bone's multi-level hierarchical structure and soft tissue, we tested whether this approach might better identify women at risk of fracture before fracture.

Design

We pooled data from three French and Swiss prospective population-based cohorts (OFELY, QUALYOR, GERICO) that collected clinical risk factors for fracture, areal BMD and distal radius measurements with high resolution peripheral quantitative tomography (HRpQCT). Using only three-dimensional images of the distal radius, ulna and soft tissue acquired by HRpQCT, an algorithm, a Structural Fragility Score-Artificial Intelligence (SFS-AI), was trained to distinguish 277 women having fractures from 1401 remaining fracture-free during 5 years and then was tested in a validation cohort of 422 women.

Setting

European postmenopausal women

Participants

We have studied postmenopausal women considered as representative of the general population, who were followed for a median 9.4 years in OFELY, 5.4 years in QUALYOR and 5.7 years in GERICO.

Main outcome and measure

All types of incident fragility fractures

Results

We used data from 2666 postmenopausal women, with age range of 42-94. In women ≥ 65 years having 'All Fragility Fractures' or 'Major Fragility Fractures', SFS-AI generated an AUC of 66-70%, sensitivities of 60-68% and specificity of 71%. Sensitivities were greater than achieved by the fracture risk assessment (FRAX) with BMD or BMD (6.7-26.7%) with lower specificities than these diagnostics (~95%).

Conclusion and relevance

The SFS-AI is a holistic surrogate of fracture risk that pre-emptively identifies most women needing prompt treatment to avert a first fracture.

Key Points

Question

Can a deep learning model (DL)^o based on high resolution images of the distal forearm predict fragility fractures?

Findings

In the setting of 3 pooled population-based cohorts, the DL model predicted fractures substantially better than areal bone mineral density and FRAX, especially in women ≥ 65 years.

Meaning

Our DL model may become an easy to use way to identify postmenopausal women at risk for fracture to improve fracture prevention.

eLife assessment

This study presents a **valuable** deep learning-based model for predicting fracture within the next five years from just a standard distal radius and ulna scan obtained using high-resolution computed tomography images. The evidence supporting the conclusion that the model-predicted fracture prediction score can be used clinically to identify women at risk of fracture more effectively than with the current standard clinical approach is **convincing**. This work will be of interest to biomechanists and biomedical engineers working on osteoporosis.

Introduction

Fragility fractures are a public health problem because fractures impose high morbidity, mortality and cost to the community.¹ To identify women with fragile bones before fracture, a W.H.O group designated women as having ‘osteoporosis’ if femoral neck bone mineral density (BMD) T-Score was ≤ -2.5 standardized deviations (SD) below the premenopausal mean.² Epidemiological studies confirmed that fracture risk increases as BMD decreases, but the frequency distribution around the age-related decline in mean BMD remains normal.

Because of this normal frequency distribution, most postmenopausal women in the community have osteopenia (T-score -2.5 to -1.0 SD) or normal BMD (T-score > -1.0 SD). These women form the source of 75% of all fragility in the community, only 25% arise among the smaller subset of women in the community with osteoporosis as defined by BMD.^{3–9} The women with osteopenia or normal BMD having fragility fractures remain unidentified and untreated using the definition of osteoporosis, a BMD T-Score ≤ -2.5 SD, to signal bone fragility. Treatment is not offered, even in the presence of a prevalent or incident fracture, because the absence of osteoporosis is incorrectly interpreted as being evidence of absence of bone fragility.¹⁰

Osteoporosis and bone fragility are used interchangeably even though they are not synonymous terms.^{11–13} Absence of osteoporosis does not exclude bone fragility. Bone fragility is not binary, present in women with osteoporosis (T-Score ≤ -2.5 SD) and absent in women without osteoporosis (T-Score > -2.5 SD). Even when bone loss only reduces BMD into the low normal or osteopenia range, the bone is unlikely to be ‘normal’. Bone mass is reduced relative to premenopausal women and many qualities of bone responsible for its strength may be compromised.^{14–18}

For example, advancing age deteriorates the composition of the mineralized matrix.^{19,20} Bone loss disrupts the spatial configuration of bone’s three-dimensional architecture.^{15,21} These changes produce a non-linear increase in bone fragility, disproportionate to both the bone loss causing the deterioration and the reduction in BMD.^{20,22} Resistance to bending is a 7th power function of bone’s cortical porosity and a 3rd power function of its trabecular density.²²

Consequently, even modest disruption of the spatial configuration of bone at nano-, and micro-levels of resolution compromise bone strength independent of BMD. In addition, soft tissue changes like loss of muscle mass (sarcopenia) impair mobility and balance predisposing to falls, fractures and mortality.²³ Thus, reducing the population burden of fractures requires a diagnostic that complements BMD by identifying women at risk of fracture due to bone fragility caused by compromised bone morphology not captured by BMD ≤ -2.5 SD, by an increased risk of

falls due to deteriorated soft tissues such as muscle mass, or both. Non-invasive evaluation of bone microarchitecture improves fracture prediction compared with FRAX plus BMD or BMD alone.^{8,9}

A promising area of innovation in the promotion of human health is the use of Artificial Intelligence (AI). Application of Deep Learning to medical imaging²⁴ facilitates the investigation of bone's multilayered qualities and has been reported to identify patients with prevalent fractures or osteoporosis in cross sectional studies.²⁵⁻²⁷ However, no prospective studies have applied deep learning using only the high resolution 3-dimensional images of bone and soft tissue to determine whether an algorithm, a Structural Fragility Score derived by Artificial Intelligence (SFS-AI), might capture deteriorated bone qualities and soft tissue. If so, this holistic surrogate of fracture risk is likely to serve as a diagnostic that pre-emptively identifies women at risk of a first or subsequent fracture needing prompt treatment and would do so better than the fracture risk assessment (FRAX) score with BMD or BMD alone.

Methods

Participants

We studied (i) 568 postmenopausal women, median age 68.2 years, range 42-94 of Os des Femmes de LYon, OFELY, France followed for a median [interquartile range] of 9.4 [1.0] years,^{9,28,29} (ii) 1427 women of the Qualité Osseuse Lyon Orléans, QUALYOR cohort (1042 recruited in Lyon, 497 in Orléans), median age 65.9 (range 50-87) years followed for 5 years³⁰ and (iii) 671 women of the Geneva Retirees Cohort, GERICO, in Switzerland median age 65 (range 63-68) years followed 5.7 years (range 2-8).³¹ The studies were approved by the institutional review boards. Participants provided informed consent. Fractures (excluding head, toes and fingers) were confirmed using radiographs.

Bone microarchitecture, bone densitometry, FRAX with BMD

HRpQCT (voxel size of 82 μm^3) was used to scan the non-dominant forearm (Scanco Medical AG, Switzerland).³² Radiation exposure was ~3 microsievert. Quality control was monitored by daily scans of hydroxyapatite rods (QRM, Moehrendorf, Germany). Femoral neck BMD was quantified using Hologic DXA scanners in the French cohorts and Hologic QDR Discovery in the Swiss cohort. T-scores were calculated using NHANES III. FRAX with femoral neck BMD provides a 10-year risk for Major Fragility Fractures (proximal humerus, wrist, distal forearm, clinical spine, or hip).³³

Deep Learning network

To avoid bias towards any one of the three cohorts, we combined the three cohorts and then we randomly divided the combined data set into a training and testing data set. No training data was used as testing data. **Figure S2** shows participants were randomly allocated to five groups, four used for training (n=1678), the fifth used for testing (n = 422). Scores were calculated for each testing group with the median forming the SFS-AI (see Supplement **Figure S2**). Deep learning was applied to images of the distal radius and ulna and the surrounding soft tissue acquired using HR-pQCT (see Supplement).³⁴⁻³⁷ Training the algorithm to identify women sustaining fractures faced two challenges: (i) extraction of features within the three-dimensional image captured by a matrix of 110*1560*1560 voxels conferring fracture risk and (ii) limited data for training predisposing to model over-fitting. We used the DenseNet121 as the feature extraction network (**Figure S1**). Features conferring fracture risk were learnt collectively by densely connected layers in the neural network. The input to the feature extraction network was the 110 slices acquired by the HR-pQCT at the distal radius (including the ulna and surrounding soft tissues). The output from the feature extraction network is a feature vector of 256 numbers.

To achieve robust feature extraction, a multi-task learning strategy was used to overcome model overfitting. To provide pictorial representation of the fracture risk prediction, extracted features were displayed as a heat map overlaid upon a 2D projection of the images. Red reflects greater relevance of the region's bone or soft tissue to fracture prediction.

Statistical Analyses

Analyses were conducted using data in women of any age and those 65 years and over. Follow-up was to fracture or freedom from fracture for five years since HR-pQCT scanning. SFS-AI, FRAX with BMD and BMD were not normally distributed and so are presented as median and interquartile range (IQR). Values are adjusted for age and cohort because of cohort differences in age and follow-up duration. (**Tables S1** and **S2**.) Comparison of the diagnostics in women having fractures and those remaining fracture-free was carried out using analysis of covariance adjusted for age and cohort and estimated by robust regression. (**Table 1** [↗](#).)

The performance of SFS-AI as a continuous trait was assessed using the area under the curve (AUC) and was estimated using a parametric probit model³⁸ [↗](#) and logistic regression to derive Odds Ratios (ORs) for fracture. Both analyses are presented unadjusted and adjusted for age and cohort effect. The sensitivity and specificity of SFS-AI as a binary trait used a threshold of 0.5. (Addressed in **Table 2** [↗](#).)

We also assessed the performance of FRAX with BMD and BMD as continuous traits using ROC analysis and computed sensitivity and specificity using thresholds of 20% for FRAX with BMD and – 2.5 SD for BMD denoting high fracture risk. Logistic regression was then used to assess any association of these diagnostics with fracture, separately and combined, for women of any age and women aged 65 years and over. (Addressed in **Figure 1** [↗](#) and **Table S3**.)

Linear regression was used to assess the association of SFS-AI with age, separately for women with fractures and women remaining fracture-free. (Addressed in **Figure 2** [↗](#).) Age, cortical porosity, trabecular density, FRAX with BMD and BMD were used in linear regression to compute an overall R-squared and to determine the proportion of variance in SFS-AI explained by these independent variables. The percentage contribution of each trait to the overall R-squared was computed using the Shapley method.³⁹ [↗](#) (Addressed in **Table S5** and **Figure 3** [↗](#).)

Results

Table 1 [↗](#) shows SFS-AI was higher in women having ‘All’ or ‘Major Fragility Fractures’ than women remaining fracture-free (both $p < 0.001$). Neither FRAX with BMD nor BMD alone differed in women having fractures versus those remaining fracture-free ($p > 0.15$).

SFS-AI pre-emptively identifies women at risk of ‘All’ and ‘Major Fragility Fractures’

Table 2 [↗](#) shows that in the testing cohort of 422 women of any age and the 236 women ≥ 65 years of age, the SFS-AI as a continuous trait generated AUCs of 73-74% for ‘All Fragility Fractures’ and ‘Major Fragility fractures’ with adjusted ORs ranging from 2.53 to 2.67 per standard deviation. The SFS-AI as a categorical trait (using a threshold of 0.5), had sensitivities ranging from 58.1% to 74.0% and specificities ranging from 71.0% to 77.3% (all significant, $p < 0.001$ for OR and AUC).

	Non-Fracture (N = 350)		All Fragility Fractures (54)			Major Fragility Fractures (N = 24)		
	Median	IQR	Median	IQR	p-value	Median	IQR	p-value
SFS-AI	0.45	0.10	0.51	0.08	<0.001	0.50	0.10	<0.001
FRAX with BMD	6.00	5.10	7.70	7.30	0.160	7.85	7.10	0.304
BMD	-1.64	0.88	-1.69	0.98	0.961	-1.77	0.75	0.292

p-values comparing women with and without incident fractures computed using robust regression adjusted for age and cohort.

Table 1

Median and interquartile ranges (IQR) for Structural Fragility Score-Artificial Intelligence (SFS-AI), Fracture Risk Assessment score (FRAX) with bone mineral density (BMD) and femoral neck BMD in women remaining fracture-free and women having Any Fragility Fractures or Major Fragility Fractures during 5 years follow-up.

		All women of any age				Women aged 65 and older			
		Any Fragility Fracture (N = 422)		Major Fragility Fracture (N = 383)		Any Fragility Fracture (N = 236)		Major Fragility Fracture (N = 208)	
		Est	95% CI	Est	95% CI	Est	95% CI	Est	95% CI
AUC	Unadjusted	0.78	(0.73, 0.84)	0.76	(0.67, 0.85)	0.78	(0.71, 0.85)	0.76	(0.63, 0.88)
	Adjusted	0.74	(0.69, 0.79)	0.73	(0.65, 0.83)	0.73	(0.67, 0.80)	0.73	(0.61, 0.84)
OR	Unadjusted	3.44	(2.47, 4.78)	2.96	(1.85, 4.76)	3.21	(2.13, 4.83)	2.82	(1.55, 5.14)
	Adjusted	2.67	(2.03, 3.51)	2.53	(1.68, 3.82)	2.64	(1.86, 3.75)	2.54	(1.49, 4.34)
Sensitivity		65.7%	(53.4%, 76.7%)	58.1%	(39.1%, 75.5%)	74.0%	(59.7%, 85.4%)	68.2%	(45.1%, 86.1%)
Specificity		77.3%	(72.5%, 81.5%)	77.3%	(72.5%, 81.5%)	71.0%	(63.9%, 77.4%)	71.0%	(63.9%, 77.4%)

N= Sample size; Est = estimate; CI = confidence interval; Area under the curve (AUC) and odds ratios (OR) estimated with SFS-AI considered as continuous measurement and unadjusted and adjusted for age and cohort effect; Sensitivity and Specificity computed using clinical cut-off point of ≥ 0.5 .

Table 2

Performance of the Structural Fragility Score-Artificial Intelligence (SFS-AI) using data in women of any age and women aged 65 years and over

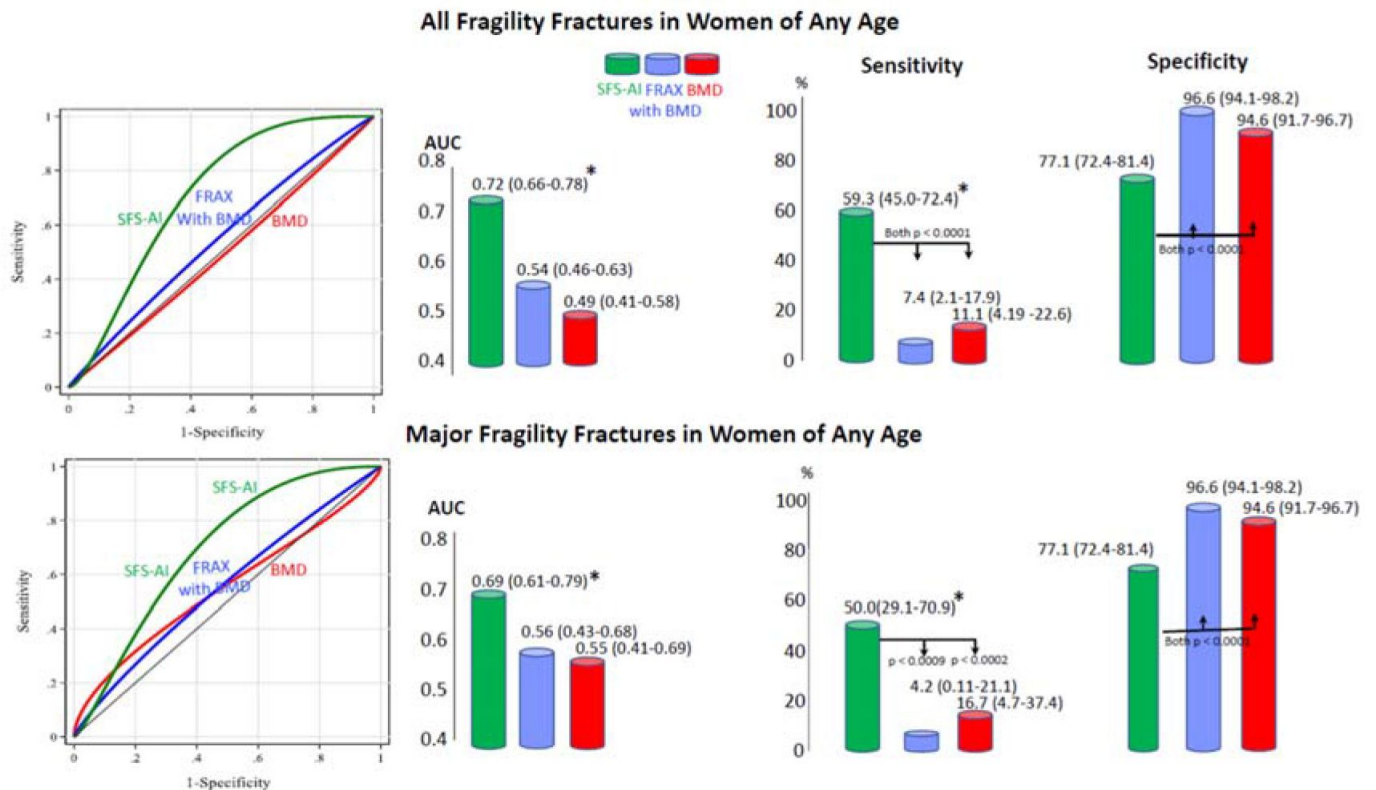


Figure 1.

Left two panels: Receiver Operator Characteristic (ROC) curves for Structural Fragility Score Artificial Intelligence (SFS-AI), Fracture Risk Assessment Score (FRAX) with bone mineral density (BMD) and BMD as a continuous trait predicting for 'All Fragility Fractures' and 'Majority Fragility Fractures' for women of any age. Area under the Curves (AUCs) with 95% Confidence Intervals (CI) were significant (* $p < 0.05$) for SFS-AI only. **Right two panels:** Sensitivity and specificity of SFS-AI, FRAX with BMD and BMD as categorical traits.

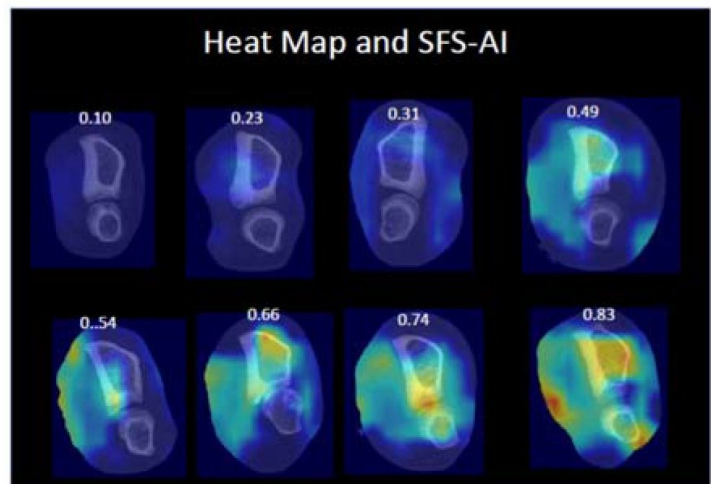
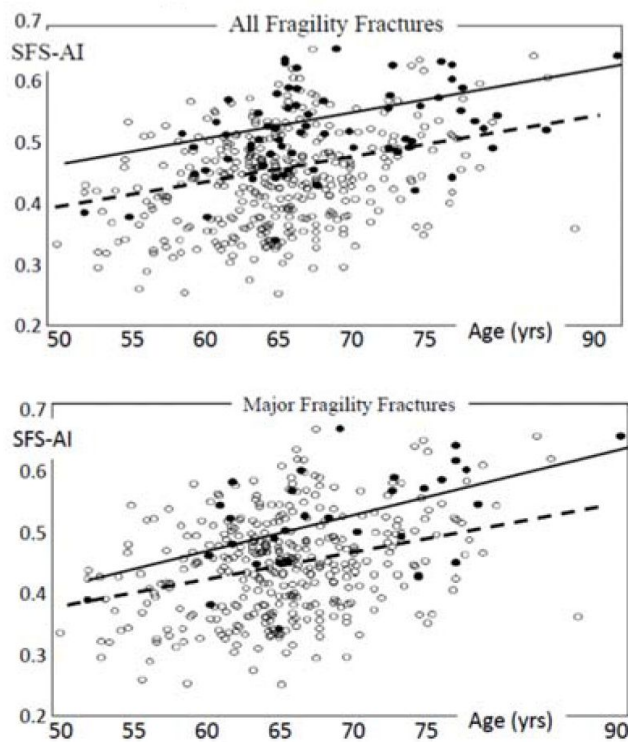


Figure 2.

Left panels: Advancing age is associated with a higher Structural Fragility Score-Artificial Intelligence (SFS-AI) in women having 'All Fragility Fractures' or Major Fragility Fractures (closed circles) and in women remaining fracture-free (open circles). The images of the distal radius and ulna with the heat map illustrate regions commonly encountered in women having fractures.

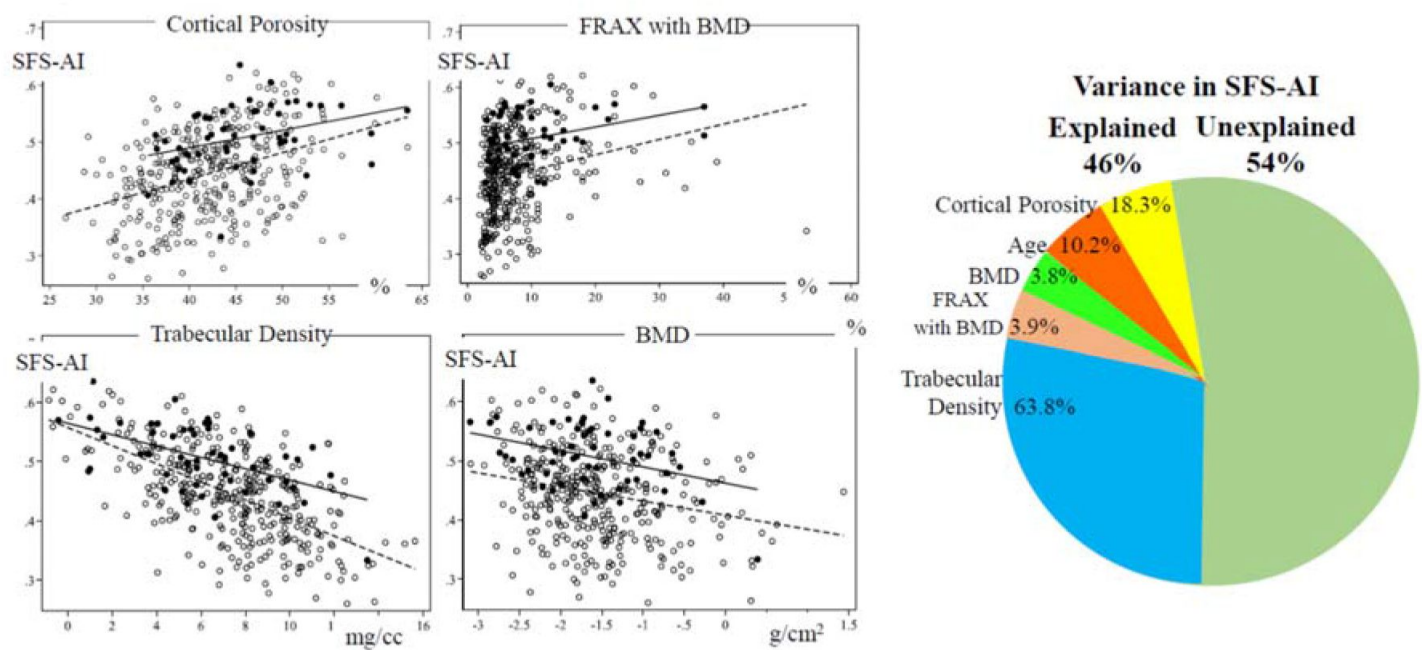


Figure 3.

Left panels. The Structural Fragility Score-Artificial Intelligence (SFS-AI) was associated directly with cortical porosity, FRAX with BMD and negatively with trabecular density and BMD. **Right diagram.** Of the 47% of explained variance in the SFS-AI, most was attributed to trabecular density, cortical porosity, age and the FRAX with BMD. The contribution of BMD was not significant. The remaining 53 percent remained unexplained.

Comparing SFS-AI with FRAX with BMD and BMD

Women of any age

Comparisons of the diagnostics was confined to participants having all three measurements. **Figure 1** shows the diagnostics as continuous traits. For ‘All Fragility Fractures’ and ‘Major Fragility Fractures’, the AUCs for SFS-AI were 72% and 69% respectively ($p < 0.05$). **Table S3** shows unadjusted and adjusted SFS-AI predicted women having either category of fractures (ORs ranged from 2.07 to 2.41, all $p < 0.001$). Neither of the other two diagnostics predicted either category of fracture. **Figure 1** also shows the diagnostics as categorical traits. For SFS-AI, sensitivities were 59.3% and 50.0% for detecting women having ‘All Fragility Fractures’ or ‘Major Fragility Fractures’ respectively, values that were significantly greater than sensitivities of FRAX with BMD or BMD (which ranged 4.2 to 16.7%). Specificities of SFS-AI were 77.1%, significantly lower than specificities of the other two diagnostics (which ranged 94.6 to 96.6%).

Women aged ≥ 65 years

Supplementary **Figure S3** shows the performance of the diagnostics as continuous traits. For ‘All Fragility Fractures’ and ‘Major Fragility Fractures’, the AUCs for SFS-AI were 70% and 66% respectively. **Table S4** shows unadjusted and adjusted SFS-AI predicted both categories of fractures (OR 1.68 to 2.15, all $p < 0.05$).

Neither of the other two diagnostics predicted either category of fracture. **Figure S3** also shows the performance of the diagnostics as categorical traits. For SFS-AI, sensitivities were 67.6% and 60.0% for detecting women having ‘All Fragility Fractures’ or ‘Major Fragility Fractures’ respectively, values significantly greater than the sensitivities of FRAX with BMD or BMD (ranging 6.67 to 26.7%). Specificities of SFS-AI were 70.7%, significantly lower than specificity of 94.6% for the other two diagnostics.

The morphological basis of the SFS-AI

Figure 2 shows that SFS-AI increased across age in women having fragility fractures and in women remaining fracture-free. Red regions of the heat map overlying bone and soft tissue identify regions of high relevance to risk of incident fractures compared to the blue regions. **Figure 3** shows that SFS-AI correlated with microarchitecture; directly with cortical porosity and FRAX with BMD, and negatively with trabecular density and BMD. **Figure 3** and Supplementary **Table S5** show that 46% of the variance in SFS-AI was explained by variance in age ($p = 0.002$), cortical porosity and trabecular density (both $p < 0.001$) but not with BMD or FRAX with BMD; 54% of the variance remained unexplained.

Discussion

A deep learning algorithm was trained to identify women having fragility fractures using only the high-resolution three-dimensional images of bone and soft tissue. No other information was used. When training no longer improved predictive strength, the algorithm was tested in a cohort without knowledge of their fracture status during the ensuing 5 years. This algorithm served as a surrogate of fracture risk, predicting the incidence of ‘All Fragility Fractures’ and ‘Major Fragility Fractures’ and did so in women 65 years and older with a sensitivity and specificity of 60-70%, outperforming BMD and FRAX with BMD, neither of which predicted fractures.

This surrogate of fracture risk, a Structural Fragility Score derived by deep learning artificial intelligence, increased across advancing age, was higher in women having incident fractures than those remaining fracture-free, and correlated directly with cortical porosity and negatively with

trabecular density. Deterioration of these two traits produces a nonlinear increase in bone fragility,²² predicts incident fractures,^{8,9} prevalent fractures⁴⁰ and predicts estimated bone strength independent of BMD.⁴¹ Deterioration of these two traits accounted for most of the 48% explained variance in SFS-AI. BMD was not an independent predictor of SFS-AI.

Many qualities of bone not captured by BMD but not yet quantifiable non-invasively, may contribute to the 54% of the unexplained variance in this surrogate of fracture risk.¹⁴⁻¹⁹ For example, heterogeneity in bone's material composition forms discontinuities, edges, that defend against fracture by increasing the energy required to initiate and propagate a crack.⁴² Small changes in the degree of mineralization increase matrix stiffness but reduce its ductility (ability to absorb energy by deforming).⁴³ Heterogeneity in the size and number of osteons,⁴⁴ the cement line around each osteon,^{45,46} the differing orientation of mineralized collagen fibres of adjacent concentric osteonal lamellae,⁴⁷⁻⁴⁹ the extent glycation,⁵⁰ hydration⁵¹ and other factors^{52,53} influence the mechanical properties of bone. The heat map implicated deterioration of soft tissue as well as bone. The nature of soft tissue deterioration is not known but if it is sarcopenia then the SFS-AI algorithm might capture a component of risk for falls.²³

Most studies using machine learning are cross sectional and examine the ability to identify persons with prevalent fractures or osteoporosis (BMD T-Score ≤ -2.5 SD).²⁴⁻²⁷ This is the first prospective study using deep learning to derive an algorithm that identifies women having incident fractures during five years. The algorithm was developed by interrogating the three-dimensional images of bone and soft tissue, no other information was used. This Structural Fragility Score serves as a surrogate of fracture risk that is likely to assist in reducing the population burden of fragility fractures. It provides a diagnostic able to identify most women at risk of fracture and provides fast processing, easy access to risk assessment allowing prompt initiation and monitoring of preventative treatment at the community level.

High resolution peripheral quantitative computed tomography (HRpQCT) technology is no-longer confined to the research domain. Commercial devices are now CE marked and FDA cleared for multiple clinical settings. Analysis requires only the acquisition of the three-dimensional image of the distal radius, ulna and soft tissue and cloud-based computer technology provides prompt diagnosis allowing initiation or monitoring of therapy.

This study has several limitations. Further studies are needed to determine whether including factors predisposing to falls such as muscle mass and function, age, height, weight and other covariates improves the performance of the diagnostic. The sample sizes were insufficient to evaluate performance of the diagnostic in predicting individual types of fracture.

Advancing age is accompanied by deterioration in bone mass, its material composition, architecture and muscle mass - factors contributing to fragility fractures, a public health problem. High-resolution quantitative computed tomography and deep learning provide a Structural Fragility Score that serves as a holistic surrogate of fracture risk. This diagnostic is an accurate, safe, rapid and easily accessible tool that captures the deterioration of bone qualities contributing to bone fragility independent of BMD and perhaps deterioration of muscle predisposing falls. This surrogate identifies women at high risk of fracture needing prompt treatment to avert fracture and may allow monitoring the success or failure of treatment.

Data Availability

Data may be made available upon reasonable request for further analysis, after examination of an analysis proposal by the investigators.

Legends for Figures in supplementary material

Figure S1. Structure of the deep learning model used to predict fracture. The input is the 110 slices of a wrist scan used to acquire the three-dimensional image of the distal radius, distal ulna and adjacent soft tissue. DenseNet121 is used as the neural network backbone. The output feature after the global average pool is a 256-dimension feature. A multi-task (age prediction, fracture prediction and non-fracture years prediction) learning strategy was used to achieve robust extraction of relevant features.

Figure S2. We studied women from OFELY (n = 568), Qualyor (n = 1427) and Gerico (n = 671). (A) There were 526, 1187 and 387 images remaining from the respective cohorts for analysis after excluding images from women remaining fracture-free followed for under 5 years and images from women having traumatic (non-fragility). (B) Women having a fragility fracture during 5 years were denoted as (+), women remaining fracture-free as (-). (C) Participants from each cohort were randomly allotted into five groups with approximately equal numbers of (+) and (-) subjects. See Methods section.

Figure S3. Left two panels. Receiver Operator Characteristic (ROC) curves for Structural Fragility Score Artificial Intelligence (SFS-AI), Fracture Risk Assessment Score (FRAX) with bone mineral density (BMD) and BMD as continuous traits predicting 'All Fragility Fractures' and 'Major Fragility Fractures' in women 65 years of age and over. Area under the Curves (AUCs) with 95% Confidence Intervals (CI) were significantly different from 0.5 (*p < 0.05) for SFS-AI only. **Right two panels.** Sensitivity and specificity of the SFS-AI, FRAX with BMD and BMD as categorical traits predicting women having 'All Fragility Fractures' or 'Major Fragility Fractures'.

Supplementary AI methods

Deep Learning Network, training and the heat map

DenseNet used dense connection between layers and achieved efficacy in feature extraction. The first layer had a 110-dimension input instead of 3-dimension input in the original DenseNet.³⁴ We added a transition layer using 1*1 convolution after the last denseblock of DenseNet to reduce the feature dimension from 1024 to 256 to extract a compact feature. A multi-task learning strategy was used to achieve more robust features. Extracted features were used to predict fractures during the ensuing 5-years, to predict the patient's age at the time of scanning and the duration of the fracture-free years of follow-up since scanning. The latter two tasks are included in the training to produce generalized feature representations powerful enough to be shared across different tasks.

We used a pretrained model as the initial model and 0.5 as the classification threshold for the training and validation. During training, cross-entropy loss was used as the fracture situation prediction loss, and used the mean squared error loss as the loss of age prediction and non-fracture year prediction. L1 regularization is performed on the weights of the classification layer to reduce overfitting. The model is optimized by ADAM optimizer using the four losses with weight 1 on the first three losses and weight 0.01 on the L1 regularization loss.³⁵ The learning rate is set as 5e-6 for the DenseNet backbone and 5e-5 for the other layers, including the transition layer and the three multi-learning branches. Pytorch is chosen to implement the model training and testing.³⁶ The Grad-CAM is utilized to generate the heatmap to represent the features that are extracted by the deep learning model.³⁷

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Reviewer #1 (Public Review):

This is an interesting study, covering a future direction for the diagnosis of osteoporosis.

Strength: well validated cohorts, authors are more than experts in the field, use of technology.

Weakness: the approach is still very experimental and far away to be clinically relevant.

The authors have performed a very interesting analysis combining data from different, well designed, cohorts.

Authors are leaders in the field. The topic is of interest, the statistical analysis well designed, and the paper is well written and easy to read even for not experts.

I have a few comments

1. Although authors are very optimistic about HRpQCT, they should recognize (and acknowledge in the discussion) that their data have a very low clinical impact for the majority of the population. The cost of the machine is still prohibitive for the majority of clinical centers, technology needs more validations out of the reference centers, a lot of controversy on the methodology for cortical porosity. Basically, after 20 years since its introduction, it remains more a research tool than a clinical opportunity. This comment is of course not against the scientific hypothesis or the conduction of the study which remain brilliant
2. How authors have managed the role of possible secondary causes of osteoporosis? Did they excluded patients with GIOP for example? Are all study subjects treatment naïve?
3. It would be worth to better describe the role of cortical porosity and the predictive value of this parameter which has been extensively studied by Dr Seeman.

Reviewer #2 (Public Review):

The authors apply a deep learning approach to predict fracture using forearm HR-pQCT data pooled from 3 longitudinal cohorts totaling 2666 postmenopausal women. The deep learning based 'Structural Fragility Score - AI' was compared to FRAX w/BMD and BMD alone in its ability to identify women who went on to fracture within the next 5 years. SFS-AI performed significantly better than FRAX w/BMD and BMD alone in all metrics except specificity. This work establishes that deep learning methods applied to HR-pQCT data have great potential for use in predicting (and therefore preventing) fractures.

The low specificity of SFS-AI compared to FRAX and BMD is not adequately acknowledged or addressed - will this lead to over diagnosis / unnecessary interventions and is that a problem?

The paper does not adequately address the relative role of bone vs soft tissue features in the determination of SFS-AI. It would be possible to feed the algorithm only the segmented bone volumes, and compare AUC, etc, of SFS-AI (bone) to that acquired using the entire bone + muscle volume. It's possible (likely?) that most of the predictive power will remain. If muscle is an important part of this algorithm, then mid-diaphyseal tibia scans will be an interesting next application - since that scan site is closer to the muscle belly compared to the distal radius site which contains very little muscle volume.

Reviewer #3 (Public Review):

This work presents a novel approach for predicting fracture risk from high-resolution peripheral quantitative computed tomography (HR-pQCT): by training a deep learning model to predict five-year fracture risk where the sole input is the full 3D HR-pQCT image. Prior studies have developed models, of varying complexity, to predict fracture risk from HR-pQCT. However, this study is novel in that neither the typical manual efforts required for HR-pQCT image analysis nor additional biomarker collection are required, simplifying potential clinical implementation. The authors show that their model predicts fracture within five years with greater sensitivity than FRAX (with an assumed diagnostic threshold of FRAX > 20% or T-score < -2.5 SD), albeit with reduced specificity. The authors further investigate how their model output, the structural fragility score derived by artificial intelligence (SFS-AI), is correlated with two microarchitectural parameters that can be measured with HR-pQCT, demonstrating that their model captures many relevant characteristics of a patient's bone quality that cannot be captured by the standard clinical tools used to diagnose osteoporosis, and thus to identify patients at elevated risk of fracture.

Strengths

The authors use a very large dataset and a combination of state-of-the-art methods for training and validating their fracture prediction model: k-fold cross-validation is used for training and a held-out external test dataset is used to evaluate ensembled model predictions compared to the current clinical standard for fracture screening. The results with the test dataset show that the model can identify women at risk of fracture in the next five years with greater sensitivity than both FRAX with BMD and BMD alone.

Because the model takes only a full 3D HR-pQCT image as input, the feasibility of clinical implementation is maximized. Standard morphological analysis with HR-pQCT is semi-automated and the labour required for the manual portions of analysis poses a significant barrier to clinical implementation. There is mounting evidence for the clinical utility of HR-pQCT (see Gazzotti et al. *Br. J. Radiol.* 2023) and fully automated models such as the one presented in this work will be critical for making clinical applications of HR-pQCT feasible.

The authors quantify the contributions to the variance of the model output and examine activation maps overlaid on the HR-pQCT images. These sub-analyses indicate that the model is identifying relevant characteristics of hierarchical bone structure for fracture prediction that are not available from aBMD measurements from DXA and thus are not accounted for in the current standard clinical diagnostic tool.

Weaknesses

The authors make the claim that SFS-AI outperforms FRAX with BMD and BMD in terms of sensitivity and specificity of predicting fragility fractures within 5 years. This claim is supported by looking at the ROCs in figure 1, but the specific comparison made in the discussion is not completely fair as currently presented in the article. The thresholds of FRAX

> 20% and T-score < -2.5SD were selected by the authors for binary comparison. FRAX and BMD achieve specificities of ~95% at these thresholds, while SFS-AI achieves a specificity of only 77% at the selected threshold, SFS-AI > 0.5. Conversely, SFS-AI achieves a sensitivity of 50% to 60% while FRAX and BMD achieve very poor sensitivities, between 4% and 16%. The authors have not justified their choice of binarization thresholds for FRAX or BMD by citing literature or clinical guidelines, nor have they motivated their choice of any of the thresholds with a discussion of how clinical considerations could influence the sensitivity-specificity trade-off. It is difficult to directly compare the prognosticative performance of SFS-AI to that of FRAX or BMD when the thresholds for FRAX and BMD are at such different locations on the respective ROCs when compared to where the threshold for SFS-AI places it on the ROC. The authors have also not compared their estimates of the sensitivity and specificity of FRAX and BMD to literature to provide important context for the comparison to SFS-AI. An additional unacknowledged limitation is that the FRAX tool is designed to predict 10-year fracture risk, while the outcome used to train the SFS-AI model and to compare to FRAX was 5-year fracture risk.

Direct comparison may be impossible due to differences in study design or reported performance metrics, but the authors have not at all discussed the quantitative performance of prior models for fracture prediction or discrimination that use HR-pQCT (see Lu et al. Bone 2023 or Whittier et al. JBMR 2023) to contextualize the performance of their novel model. While the model presented in this article has the advantage that it does not require the typical expertise and manual effort needed for HR-pQCT image analysis, it is still important to acknowledge the potential trade-off of ease of implementation vs performance. Models that incorporate additional clinical data or that use standard HR-pQCT analysis outputs rather than raw images may perform well enough to justify the increase in the difficulty of clinical implementation or to motivate further work on fully automating microarchitectural analysis with HR-pQCT images.

Finally, the article does not indicate that either the code used for model training or the trained model itself will be made publicly available. This limits the ability of future researchers to replicate and build on the results presented in the article.