Digital Wrist Tomosynthesis-Based Radiomics Differentiates Patients With and Without Osteoporotic Fracture

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INTRODUCTION: Bone fracture due to osteoporosis is a growing health concern in the aging population. Bone mineral density (BMD), the gold standard for assessing osteoporosis status, has limited accuracy in the assessment of fracture risk. Bone qualities additional to BMD improve the accuracy in predicting fracture risk. Radiomics, which provides a comprehensive set of image features at different scales, has shown promise for osteoporosis screening and fracture prediction using DXA, MRI, and CT. However, utilization of these modalities is limited due the high cost and radiation dose and lack of adherence to recommendations for bone health screening. Recently, digital wrist tomosynthesis (DWT) using a digital breast tomosynthesis scanner during a mammography visit has been suggested as an alternative bone health assessment procedure due to its high resolution, low radiation dose, and particularly to its availability during breast cancer screening [1]. However, the utility of radiomics in DWT has not yet been explored. Therefore, the goals of the current study were 1) to establish the repeatability of DWT-based radiomic features, 2) to determine the extent to which DWT-based radiomics distinguish between patients with and without osteoporotic fracture, and 3) to determine whether the radiomic features are associated with fracture status independently of BMD.

METHODS: Under IRB approval 134 osteoporotic and osteopenic women (age:50-88years) with (Fx: n=49) or without (NFx: n=85) osteoporotic fracture were recruited. This study included only women due to the higher fracture prevalence and the study setting in a mammography clinic. DXA-based BMD were measured for each participant at hip, femoral neck, spine and forearm. The nondominant arm of each participant was DWT scanned using a breast tomosynthesis scanner (GE Senographe Essential). Nine projection images of the forearm were taken over 25^0 at 35 kV and 50 mAs and reconstructed at 0.1 x 0.1 mm pixel size in the frontal plane with 1 mm slice thickness. From the DWT image, an ultra-distal (UD) volume of 8 central slices (8 mm in depth), 15 mm in length, was extracted proximal to the 10 mm offset from the ulnar styloid process [1]. A global threshold was utilized to delineate the radius bone from surrounding soft tissue and then region was resampled at isotropic voxel size 0.1 mm. A total of 1037 3D radiomic features – 107 derived from the original (unprocessed) images, 186 from Laplacian of Gaussian (LOG) filtered images (radius 1 and 3), and 744 from wavelet-filtered images – were extracted using PyRadiomics 3.0.1 in Python (Figure 1). To select reliable features, 6 participants were scanned thrice in the same scanner and image analysis was performed using the same protocol as mentioned above. Repeatability of radiomic features were quantified as the percent root mean square coefficient of variation ($\%CV_{RMS}$). Radiomic features having a $\%CV_{RMS} \leq 5$ were included for further analysis [2]. Later, Wilcoxon tests were used to compare Fx and NFx groups, and variables with a p-value < 0.05 were retained for further analysis [3]. Further, principal component analysis with Varimax rotation was performed to extract orthogonal factors, and top features with a loading factor > 0.7 were identified for constructing multivariable logistic regression models. To avoid multicollinearity, models with a variance inflation factor (VIF) ≥ 5 were excluded during the construction of forward stepwise regression models. The model's discriminative ability was assessed using the area under the Receiver Operating Characteristic (ROC) curve (AUC), and the best model was identified as one with the highest AUC. To investigate the contribution of radiomic features independent of BMD, participants from the Fx and NFx groups were 1:1 matched on hip BMD, femoral neck BMD, and BMI using nearest-neighbor propensity score obtained through logistic regression analysis. The aforementioned logistic regression and PCA analyses were subsequently repeated on this matched dataset. The PCA was performed in JMP, and all other statistical analysis were performed in R.

RESULTS: Among 1037 radiomic features, 437 had $CV_{RMS} \leq 5\%$. For the unmatched dataset, age and BMI were not different between Fx and NFx groups (p>0.3). BMD at the hip, femoral neck and TBS of the spine were significantly lower (p<0.02), while BMD of spine and UD radius were marginally lower (0.05<p<0.1) in Fx compared to NFx. The best DXA-based model for predicting Fx status included hip BMD and TBS (AUC=0.671, p<0.04 and p<0.02, respectively) for the nonmatched dataset, while TBS was the only significant predictor among the DXA variables in the BMD-matched dataset (AUC=0.623, p<0.04). Among 437 highly repeatable radiomic features, 39 were significantly different between the Fx and NFx groups. Four factors identified through PCA were associated with bone density, texture heterogeneity at fine scale, textural heterogeneity at coarse scale, and directional heterogeneity. Factors 1, 2 and 4 were significantly associated with fracture status (AUC=0.705, p<0.004 to p<0.025). The model with the highest AUC (0.740, Figure 2) contained one feature from each significant factor: original_10^{th} percentile (p<0.006) from factor 1 and LoG-3_contrast (p<0.02) from factor 2, negatively associated with fracture, and wavelet-LLH_skewness (p<0.009) from factor 4, positively associated with fracture (Figure 1). For the BMD-matched dataset, factor 1 (associated with bone density), as would be expected, was not significantly associated with fracture status (p>0.1). Factors 2 and 4 remained significant predictors of fracture status and together yielded a model with AUC=0.703 (p<0.03 and p<0.007, respectively). The best model using the radiomic variables contained LoG-3_difference variance (p<0.001, factor 2) and wavelet-LLH_skewness (p<0.004) (AUC=0.753, Figure 2) for the BMD-matched dataset.

DISCUSSION: 42% of DWT-based radiomic features have high repeatability, which lies within the range from other imaging modalities such as MRI, and radiography (37–58%) [2]. There is limited research on the use of radiomics for predicting "any osteoporotic" fracture in the general population. Nonetheless, the fracture prediction accuracy of DWT-based radiomics lies within the range for DXA based radiomic models of "any osteoporotic" fracture, that combines radiomic features measured from multiple sites (such as hip and spine) in diabetic patients with or without kidney disease (AUC: 0.739-0.844) [4, 5]. The composition of the four orthogonal factors from PCA indicates that bone density, textural heterogeneity at both fine and coarse scales, and directional heterogeneity are distinct features of bone microstructure. The radiomic features included in the model of fracture with the highest AUC (Figure 2) suggest that in addition to lower density, homogenous texture at fine scales, and heterogeneity of coarse structures in the dorso-palmar direction at the ultra-distal radius are also associated with higher odds for fracture. This finding is concurrent with other studies which reported textural homogeneity is negatively associated with bone strength [6] and fracture status [7]. In conclusion, DWT imaging can capture not only overall bone density but also other textural features, which can be utilized for a more accurate bone health screening. Future work is needed to further establish the utility of the current radiomics-based models from DWT using independent cohorts.

CLINICAL RELEVANCE: This study shows that DWT-based radiomic features can capture key aspects of bone qualities, including density and textural heterogeneity at different scales, that are relevant to fracture status. Incorporating these features in DWT may improve the accuracy of fracture prediction while at the same time enhancing adherence to bone screening recommendations.

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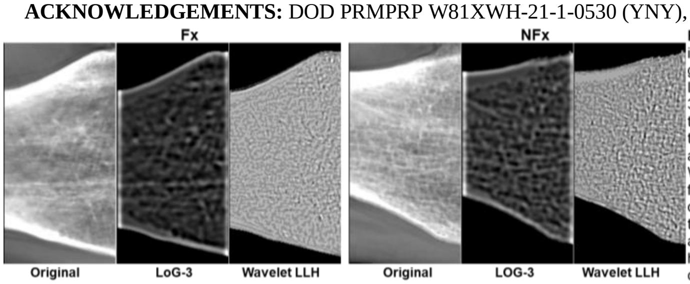

Figure 1. Representative wrist images from Fx and NFx groups, including the original, Laplacian of Gaussian (radius = 3) filtered (LoG-3), and wavelet-transformed image (low-pass in the frontal plane and high-pass along the palmer-dorsal axis, Wavelet-LLH). Participants with fractures show lower bone density (original), reduced textural heterogeneity (LoG-3), and increased directional heterogeneity (Wavelet-LLH) compared to controls.

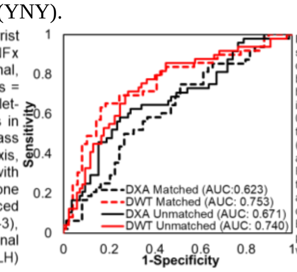

Figure 2. ROC curves for predicting fracture status in BMD-matched and BMD-unmatched datasets. In the unmatched dataset, the DWT-based radiomic model (density, fine scale heterogeneity, directional heterogeneity) identified patients with fracture status with AUC 0.74 vs 0.67 for DXA (hip BMD and TBS). In the BMD-matched dataset, the radiomic model (fine scale and directional heterogeneity) achieved an AUC 0.75 vs 0.62 for TBS. Furthermore, AUCs were comparable between the DWT-based models for the BMD-matched and unmatched datasets, suggesting that DWT-derived textural variables are independent of BMD and that, despite having similar BMD, patients with compromised texture may still be vulnerable to bone fracture.