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RESEARCH ARTICLE

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A Fracture Risk Assessment Tool for High Resolution Peripheral Quantitative Computed Tomography

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ABSTRACT

Most fracture risk assessment tools use clinical risk factors combined with bone mineral density (BMD) to improve assessment of osteoporosis; however, stratifying fracture risk remains challenging. This study developed a fracture risk assessment tool that uses information about volumetric bone density and three-dimensional structure, obtained using high-resolution peripheral quantitative compute tomography (HR-pQCT), to provide an alternative approach for patient-specific assessment of fracture risk. Using an international prospective cohort of older adults ($n = 6802$) we developed a tool to predict osteoporotic fracture risk, called μFRAC. The model was constructed using random survival forests, and input predictors included HR-pQCT parameters summarizing BMD and microarchitecture alongside clinical risk factors (sex, age, height, weight, and prior adulthood fracture) and femoral neck areal BMD (FN aBMD). The performance of μFRAC was compared to the Fracture Risk Assessment Tool (FRAX) and a reference model built using FN aBMD and clinical covariates. μFRAC was predictive of osteoporotic fracture (c-index = 0.673, $p < 0.001$), modestly outperforming FRAX and FN aBMD models (c-index = 0.617 and 0.636, respectively). Removal of FN aBMD and all clinical risk factors, except age, from μFRAC did not significantly impact its performance when estimating 5-year and 10-year fracture risk. The performance of μFRAC improved when only major osteoporotic fractures were considered (c-index = 0.733, $p < 0.001$). We developed a personalized fracture risk assessment tool based on HR-pQCT that may provide an alternative approach to current clinical methods by leveraging direct measures of bone density and structure. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: FRACTURE PREDICTION; RISK ASSESSMENT; MACHINE LEARNING; BONE MICROARCHITECTURE; HIGH RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY; OSTEOPOROSIS

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Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture.[1,2] Femoral neck areal bone mineral density (FN aBMD), measured using dual-energy X-ray absorptiometry (DXA), serves as a good proxy for bone strength, explaining up to 70% of the variation.[3] Consequently, for the past two decades FN aBMD has been the mainstay for clinical diagnosis of osteoporosis; a patient is defined as osteoporotic if their FN aBMD is 2.5 standard deviations below the mean value of young healthy female population (ie, *T*-score < -2.5).[4,5] However, aBMD does not account for structural characteristics that contribute to bone strength, such as reduced trabecular connectivity, cortical thinning, and increased porosity.[2] This deficiency likely explains why FN aBMD lacks sensitivity in diagnosis, and, in part, why the majority of osteoporotic fragility fractures occur in individuals who do not have osteoporosis based on BMD testing criteria (eg, a *T*-score threshold of -2.5).[6–9]

The suboptimal stratification of fracture risk by aBMD alone led to the development of statistical prediction models that incorporate clinical risk factors known to have associations with fracture risk independent of aBMD, documented through meta-analyses and population studies.[5,10–12] Over 48 fracture risk assessment tools that use a combination of clinical risk factors, FN aBMD, or public health registries been developed worldwide.[13,14] The most established of these are the Garvan Fracture Risk Calculator,[15] the QFracture Risk Calculator,[16] and the Fracture Risk Assessment Tool (FRAX).[17] These three tools utilize between four and 26 clinical risk factors either in combination with aBMD or independently to provide a probability of fracture. However, the use of clinical risk factors is an indirect approach to capturing bone quality and fall risk, and is reliant on patient recall, accurate medical records, and physician discretion.

With the advent of high-resolution peripheral quantitative computed tomography (HR-pQCT), it is possible to noninvasively assess key elements of bone strength, namely compartment-specific volumetric BMD, macrostructure, and microarchitecture at the appendicular skeleton.[18] When HR-pQCT is combined with micro finite element (μFE) analysis it can provide a patient-specific estimate of bone strength.[19,20] Although HR-pQCT imaging is limited to peripheral sites such as the radius and tibia, it has been established through meta-analyses and large multicenter prospective studies that HR-pQCT predicts fracture risk independently of FN aBMD.[21,22] However, synthesizing the numerous parameters provided by HR-pQCT to arrive at an estimate of fracture risk remains a challenge. Strategies used to date include assessing parameters individually, or use of traditional statistical models (such as Cox proportional hazard regression) built on a subset of HR-pQCT parameters.[22] These approaches are limited in their ability to synthesize the complex relationships between density and structural characteristic that underpin bone strength. Supervised machine learning offers an alternative approach to predictive modeling that is highly flexible due to its less restrictive assumptions, and is capable of modeling complex high-dimensional data. Recent advances have extended supervised machine learning techniques beyond classification and regression algorithms to handle right-censored survival data,[23–25] which is necessary for modeling prospective fracture risk. These advances in predictive machine learning coupled with the wealth of information about bone characteristics offered by HR-pQCT provide a promising approach to improve fracture risk assessment when compared with methods using DXA and clinical risk factors.

The objective of this study is to develop a fracture risk assessment tool using HR-pQCT data and apply supervised machine learning methods to improve stratification of fragility fracture risk. The tool is developed to supplement DXA-based FN aBMD and common clinical risk factors, but is also proposed as a stand-alone tool capable of substituting for DXA imaging and minimizing reliance on clinical risk factors.

Subjects and Methods

Participants

Female and male participants with individual-level data were obtained from the Bone Microarchitecture International Consortium (BoMIC), a large international HR-pQCT dataset with prospective fracture information.[22] The BoMIC participants used in this study originate from seven international cohorts: the Framingham Study[26] and Mayo Clinic[27] in the United States; the Qualité Osseuse Lyon Orléans (QUALYOR),[28] Structure of Aging Men's Bones (STRAMBO),[29] and Os des Femmes de Lyon (OFELY)[30] in France; the Geneva Retirees Cohort (GERICO)[31] Switzerland; and the Canadian Multicentre Osteoporosis Study (CaMos) in Canada.[32] The Swedish Osteoporotic Fractures in Men Study (MrOS)[33] cohort in the BoMIC dataset was not used because participant-level information was not available.[22] All participants provided written informed consent for their respective cohort study, and the Institutional Review Board for Human Research at Hebrew SeniorLife approved this study.

Fracture outcomes

Participants were followed from the time of their HR-pQCT scans until either an incident fracture occurred, death, last contact, or the cohort's study closing date. Incident fractures are queried at study visits and medical professionals and trained research staff confirm reported fractures by the review of medical records, including surgical reports, discharge summaries, and X-ray reports.[22] The primary outcome of this study was the time to first fracture, which included the shoulder/collar, upper arm, elbow, upper forearm, wrist/lower forearm, hand, rib, spine, coccyx, pelvis, hip, lower thigh, knee, shin, ankle, foot, and heel. Pathologic fractures, radiographic vertebral fractures not clinically detected, and high-trauma fractures were excluded. A secondary outcome was the time to first major osteoporotic fracture (MOF) site, which included the upper forearm/wrist, humerus, hip, and spine. In the secondary analysis of MOF events, participants who sustained an incident fracture at a non-MOF site were right censored as fracture information after the first fracture event was not captured.

Baseline data collection

At baseline, height and weight were measured with standard methods, and participants completed questionnaires regarding descriptive characteristics, prior adulthood fracture history, and current use of osteoporosis medication. Participants were scanned at the distal radius and tibia using HR-pQCT (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland) following standard *in vivo* protocol for scan acquisition and analysis,[34] as previously described in detail.[22] The resulting density and morphological parameters were obtained at the radius and tibia: total, cortical,

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and trabecular BMD (Tt.BMD, Ct.BMD, and Tb.BMD, respectively); total, cortical, and trabecular cross-sectional areas (Tt.Ar, Ct.Ar, and Tb.Ar, respectively); derived cortical thickness (Ct.Th[d]); trabecular number (Tb.N); and trabecular inhomogeneity (Tb.1/N.SD). Failure load was defined as the load when 2% of the bone volume exceeded a critical strain of 0.7%,[20] and was estimated using linear μFE analysis using axial compression conditions with a 1% apparent strain. Estimated failure load obtained from individual cohorts were standardized using previously reported linear calibration equations.[35] All HR-pQCT images were graded for motion artifacts, and scored on a scale from 1 (no motion) to 5 (high motion).[36] Scans with a motion score of 4 or more were excluded from analysis.

FN aBMD was measured for all participants using either Hologic (Hologic, Marlborough, MA, USA) or Lunar (GE Healthcare, Madison, WI, USA) DXA scanners, depending on the study site, and was standardized across DXA systems using previously reported equations.[37] The FRAX score with aBMD for 10-year MOF risk was calculated for each cohort using the tool calibrated for their region, where inputs included femoral neck areal BMD and 11 other clinical risk factors (age, sex, weight, height, previous fracture, parental hip fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and alcohol consumption).[17] Prior adulthood fractures included any fractures that occurred throughout adulthood, excluding fractures of the skull, finger, toe, hand, foot, and ankle, and pathological fractures. FRAX scores were missing or not calculated for 132 (1.9%) of participants due to missing FN aBMD, height or weight information. For any other missing categorical clinical risk factors, the FRAX algorithm assumes an input of "no".[38] A total of 27 (0.4%) of participants, obtained from the CaMos cohort, had missing information on "secondary osteoporosis". However, "secondary osteoporosis" does not change the calculated risk when FN aBMD is provided.[39] In the Framingham Study, information was missing on rheumatoid arthritis for 28 individuals, and information was missing on parental history of hip fracture

Table 1. Descriptive Statistics for Participants at Baseline With and Without Any Incident Nontraumatic Osteoporotic Fracture

	Missing (%)[a]	No incident fracture ($n = 6092$)	Incident fracture ($n = 609$)[b]	p
Sex (female)	0.0	1396 (69%)	488 (80%)	<0.01
Age (years)	0.0	67.9 ± 8.8	69.3 ± 8.9	0.02
Any previous adulthood fracture	0.1	1396 (23%)	202 (33%)	<0.01
Current osteoporosis medication	0.2	664 (11%)	106 (17%)	<0.01
Follow-up time (years)[c]	0.0	4.8 ± 2.3	3.3 ± 2.3	<0.01
Anthropometrics				
Height (cm)	0.1	163.6 ± 8.6	162 ± 8.1	<0.01
Weight (kg)	0.1	71.5 ± 15.6	68 ± 13.6	<0.01
DXA and FRAX				
Femoral neck areal BMD (g/cm^2)	1.6	0.80 ± 0.13	0.75 ± 0.12	<0.01
FRAX 10-year MOF risk (%)	2.0	8.5 ± 6.1	11.0 ± 8.4	<0.01
HR-pQCT – radius				
Total BMD (mg HA/cm^3)	9.4	298.5 ± 67.6	264.0 ± 65.9	<0.01
Cortical BMD (mg HA/cm^3)	9.4	835.2 ± 76.7	810.6 ± 83.6	<0.01
Trabecular BMD (mg HA/cm^3)	9.4	152.1 ± 41.6	128.8 ± 41.9	<0.01
Trabecular number (1/mm)	9.4	1.82 ± 0.37	1.60 ± 0.37	<0.01
Trabecular inhomogeneity (mm)	9.4	0.25 ± 0.18	0.32 ± 0.23	<0.01
Cortical thickness[d] (mm)	9.4	0.71 ± 0.21	0.63 ± 0.20	<0.01
Total area (mm^2)	9.4	290.1 ± 76.0	283.5 ± 71.3	0.31
Cortical area (mm^2)	9.4	51.7 ± 17.1	44.6 ± 14.4	<0.01
Trabecular area (mm^2)	9.4	230.8 ± 68.9	230.1 ± 66.5	1.00
Failure Load (N)	10.1	2295 ± 715	1939 ± 584	<0.01
HR-pQCT – tibia				
Total BMD (mg HA/cm^3)	2.6	271.6 ± 56.7	244 ± 53.3	<0.01
Cortical BMD (mg HA/cm^3)	2.6	812.3 ± 72.7	787.1 ± 77.5	<0.01
Trabecular BMD (mg HA/cm^3)	2.6	162.1 ± 39.1	145.0 ± 36.0	<0.01
Trabecular number (1/mm)	2.6	1.78 ± 0.38	1.60 ± 0.35	<0.01
Trabecular inhomogeneity (mm)	2.6	0.25 ± 0.15	0.32 ± 0.26	<0.01
Cortical thickness[d] (mm)	2.6	1.02 ± 0.31	0.90 ± 0.28	<0.01
Total area (mm^2)	2.6	731.3 ± 148.9	721.3 ± 133.3	1.00
Cortical area (mm^2)	2.6	108.9 ± 35.1	94.5 ± 29.8	<0.01
Trabecular area (mm^2)	2.6	612.8 ± 140.8	615.1 ± 131.1	0.61
Failure load (N)	4.4	5880 ± 1559	5129 ± 1274	<0.01

Continuous parameters are reported as mean ± standard deviation and nominal parameters are reported as frequency and percentage.

BMD = bone mineral density; HR-pQCT = high-resolution peripheral quantitative computed tomography; DXA = dual-energy X-ray absorptiometry; FRAX = fracture risk assessment tool; MOF = major osteoporotic fracture.

[a]Missing values include images that were excluded due to high motion scores.

[b]Excludes high-trauma fractures ($n = 101$, 1.5% of the population).

[c]Follow-up time is the time to either an incident fracture occurred, death, last contact, or the cohort's study closing date first incident of: osteoporotic fracture, death, study close date, or lost to follow-up.

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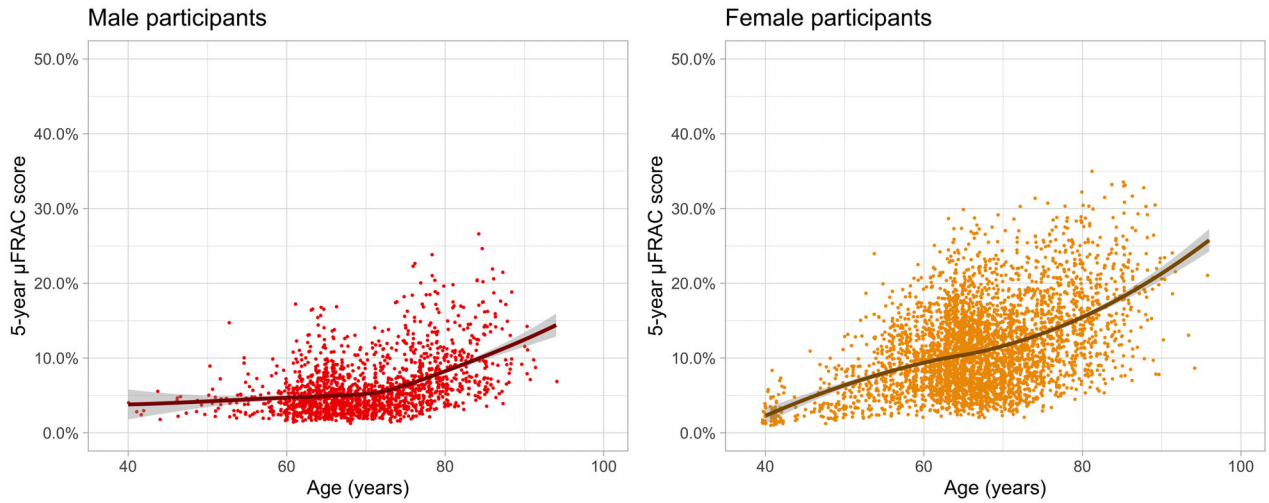

Fig. 1. The µFRAC 5-year predicted risk of any osteoporotic fracture in males (left) and females (right) relative to age. The smoothed line and shaded region represent the fitted LOWESS (locally weighted scatterplot smoothing) curve and 95% confidence intervals for the relationship between 5-year osteoporotic fracture risk and age.

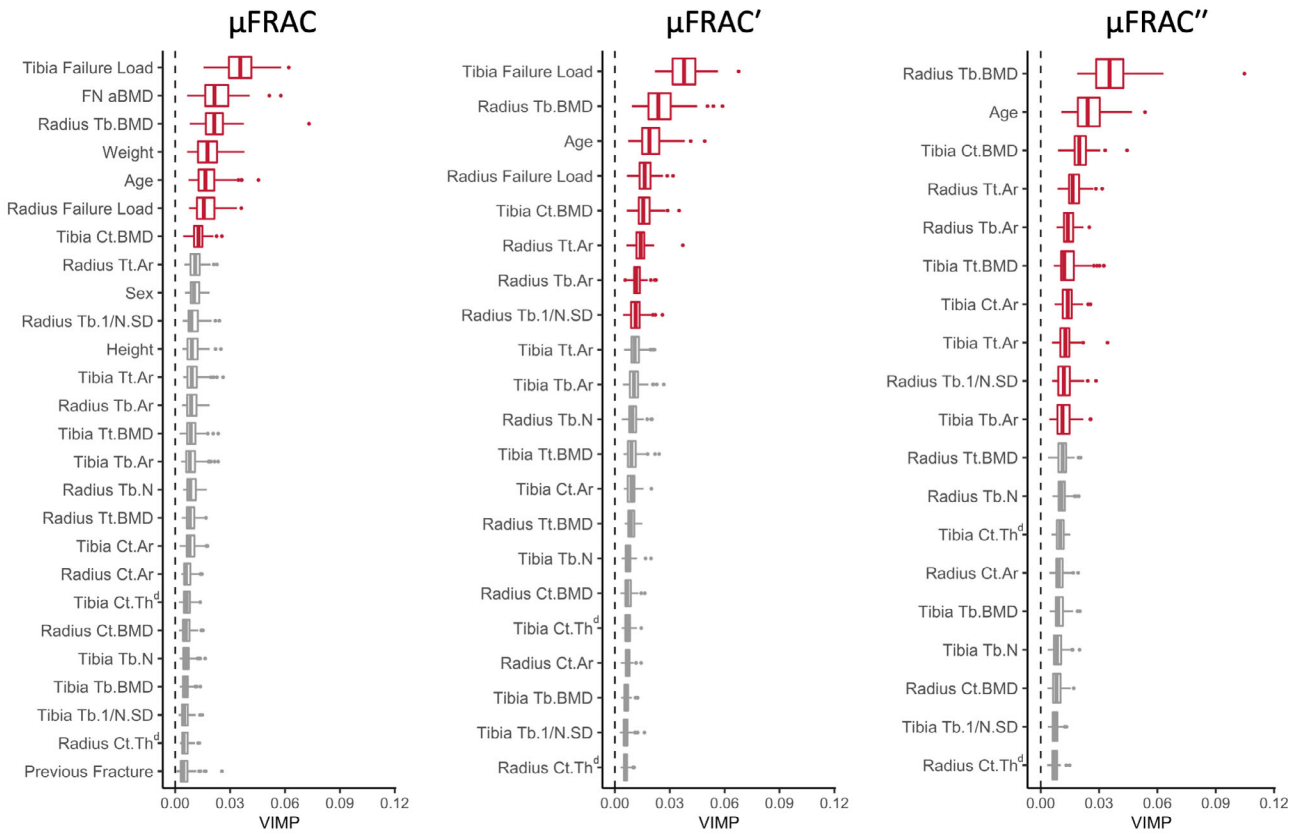

Fig. 2. Variable importance (VIMP) for the complete and simplified µFRAC models to predict any osteoporotic fracture. The boxplots represent the distribution of VIMP score for each parameter across the 100 bootstrap iterations, and parameters are sorted from highest to lowest VIMP within each model. The dashed line represents zero VIMP, and the parameters colored in red have a VIMP above the overall mean of the complete µFRAC model (0.012), illustrated for comparison purposes. FN aBMD is femoral neck areal bone mineral density; Tt.BMD, Ct.BMD, and Tb.BMD are total, cortical, and trabecular bone mineral density, respectively; Tb.N and Tb.1/N.SD are trabecular number and inhomogeneity respectively; $Ct.Th^d$ is derived cortical thickness; and Tt.Ar, Ct.Ar, and Tb.Ar are total, cortical, and trabecular, respectively.

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for 858 individuals, totaling 13.0% of all BoMIC participants. Thus, FRAX scores may have been underestimated for a subset of these participants with missing information and were misclassified with a "no" response to these risk factors.

Predictive modeling

The fracture risk assessment tool for HR-pQCT, termed the Microarchitecture Fracture Risk Assessment Calculator (μFRAC), was developed using random survival forests, an ensemble tree-based supervised machine learning method developed for right-censored survival data.[23] In contrast to Cox proportional hazard regression, which is a traditional semiparametric statistical modeling approach, random survival forests is fully nonparametric with less restrictive assumptions. Characteristics that make random survival forests ideal for modeling with HR-pQCT data include minimal data preprocessing, no assumption of the relationships or prior knowledge of interactions between input parameters, robustness to outliers, and the ability to easily handle high-dimensional data.[23] In addition, the contribution of each parameter to model prediction can be quantified using an assessment of variable importance, allowing for inference of how the model is utilizing predictors.[40] The output of μFRAC is a patient-specific cumulative hazard function,[23] which can be used to estimate time-specific (5-year and 10-year) probabilities of fracture.

The μFRAC model was initially constructed using HR-pQCT parameters and μFE-estimated failure load at the radius and tibia, FN aBMD measured using DXA, and the following clinical risk factors: sex (male/female), age, height, weight, and occurrence of any prior adulthood fracture (yes/no). Two additional μFRAC models were constructed to determine if the DXA and clinical risk factors were necessary to achieve good fracture prediction: (i) removal of FN aBMD and all clinical risk factors except for age, and (ii) additional removal of μFE-estimate failure loads of the radius and tibia. The reduced models are termed μFRAC′ and μFRAC″, respectively, and were developed to offer simplified models that included only parameters that are currently integrated into the standard HR-pQCT workflow.

In all cases participants with missing data required for each model were removed. Imputation was not explored as HR-pQCT data from a single scan site is rarely partially complete, except for μFE-estimated failure load. All models were trained and validated using bootstrap sampling, over 100 iterations drawn with replacement. This approach results in approximately 63% of the dataset being sampled for training, whereas the remaining 37% is held for validation in each iteration. The optimal split at each tree node was determined using the gradient-based Brier score technique,[23] and hyperparameters were tuned using a grid search approach within the training set of each bootstrap iteration. Tuned hyperparameters include the number of trees, minimum terminal node size, and number of random candidate parameters selected for node splitting. Constraints and step size for the grid search were set manually with consideration of computation time and model performance (Table S1).

Table 2. Overall Predictive Performance of μFRAC and Reference Models

		Any osteoporotic fracture			Major osteoporotic fracture		
Model	Model predictors	Number of participants[a]	c-index (95% CI)	Difference[b]	Number of participants[a]	c-index (95% CI)	Difference[b]
Microarchitecture fracture risk calculators (μFRAC)							
μFRAC	HR-pQCT,[c] failure load, FN aBMD, and covariates[d]	5702	0.673 (0.669, 0.676)[e]	0.037	5750	0.733 (0.729, 0.738)	0.044
μFRAC′	HR-pQCT, failure load and age	5792	0.668 (0.664, 0.671)[e]	0.032	5841	0.722 (0.718, 0.726)[f]	0.033
μFRAC″	HR-pQCT and age	5925	0.659 (0.656, 0.662)	0.023	5976	0.715 (0.711, 0.719)[f]	0.026
Reference models							
Reference aBMD model	FN aBMD and covariates	6585	0.636 (0.632, 0.640)	Reference	6644	0.689 (0.684, 0.694)	Reference
FRAX	FRAX (calculated with FN aBMD)	6570	0.617 (0.614, 0.621)	−0.019	6629	0.658 (0.653, 0.662)	−0.031

Note: All models were significantly different from one another after post hoc comparisons (adjusted $p < 0.01$), unless indicated otherwise.

Abbreviations: μFRAC = microarchitecture fracture risk assessment tool; FN aBMD = femoral neck areal bone mineral density; FRAX = fracture risk assessment tool.

[a]Participants were excluded only if one or more input parameters needed for modeling were missing.

[b]Differences between model c-indices are relative to the reference aBMD model, where a positive difference indicates improved performance.

[c]HR-pQCT Includes density and microarchitecture parameters output from the standard analysis of both scans sites (radius and tibia).

[d]Covariates include age, sex, height, weight, and prior adulthood fracture.

[e]Post hoc comparison between μFRAC and μFRAC′ was not significantly different for any osteoporotic fracture (adjusted $p = 0.24$).

[f]Post hoc comparison between μFRAC′ and μFRAC″ was not significantly different for MOF (adjusted $p = 0.18$).

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Variable importance (VIMP) within the three versions of the μFRAC models was assessed using the Breiman-Cutler approach to quantify predictiveness of individual parameters.[41] Large VIMP values are indicative of variables with greater predictive ability, whereas zero or negative values represent nonpredictive parameters. Outcomes of VIMP analysis for the complete μFRAC model were used to determine what clinical risk factors would be removed for the subsequent simplified models.

Performance of the μFRAC models was compared against the FRAX tool and a reference model based on FN aBMD and common clinical risk factors to represent expected performance of other clinical tools, such as the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) system of fracture assessment.[42] Femoral neck aBMD and clinical risk factors (sex, age, height, weight, and prior adulthood fracture) were used as input parameters for the reference model, and modeling was performed using traditional Cox proportional hazard regression. All continuous parameters were standardized and the linearity assumption checked by plotting the martingale residuals against continuous parameters.[43] Input parameters were log-transformed where necessary to meet the linearity assumption and the proportional hazards assumption was checked using the Schoenfeld's residual correlation test.[44] Finally, parameter selection for the model was performed using least absolute shrinkage and selection operator (LASSO), a modern variable selection approach.[45,46] The model was trained and tested using the equivalent bootstrap sampling implemented for μFRAC models.

Statistical analysis and evaluation of model performance

Descriptive statistics grouped by participants with and without any incident osteoporotic fracture were determined. Differences between groups were compared using the chi-squared test for categorical parameters, and Wilcoxon rank sum test for continuous parameters.

Overall performance in predicting risk of any osteoporotic fracture or MOF by the μFRAC, FRAX, and the reference aBMD models was estimated using Harrell's concordance index (c-index) that takes into account censoring.[47] In addition, 5-year and 10-year receiver operator characteristic (ROC) curves were generated and area under the curve (AUC) estimated to assess predictive accuracy of fracture at each of these time intervals. The mean and 95% confidence intervals (CI) for the c-index and time-specific AUCs of each model were estimated from bootstrap sampling results. The c-indices and time-specific AUCs of all models were compared for significant differences using a one-way analysis of variance (ANOVA), and Tukey tests were performed for post hoc comparisons.[48] All analysis was implemented in R (v3.4.1), the randomForestSRC (v2.10) and glmnet (v4.1) packages were used to develop the μFRAC and reference aBMD model, respectively. Significance was set to $p < 0.05$ for all statistical tests.

Results

The BoMIC cohort comprised of 6802 individuals (71% female) who were followed for a mean duration of 4.7 ± 2.4 years, amounting to 31,690 person-years (Table S2). During follow-up 609 (9.0%) nontraumatic osteoporotic fractures occurred, of these 324 (4.8%) were at MOF sites. Descriptive characteristics, clinical risk factors, and medical imaging data of individuals with and without an incident nontraumatic osteoporotic fracture are presented (Table 1). Significant groupwise differences between those with and without incident osteoporotic fractures were found across all metrics except Tt.Ar and Tb.Ar at the radius and tibia. When stratified by sex, differences in height and weight were no longer significant for females with and without incident fracture, whereas differences in height, FRAX score, prior fracture, and current osteoporosis medication use were no longer significantly different between males with and without incident fracture (Tables S3 and S4).

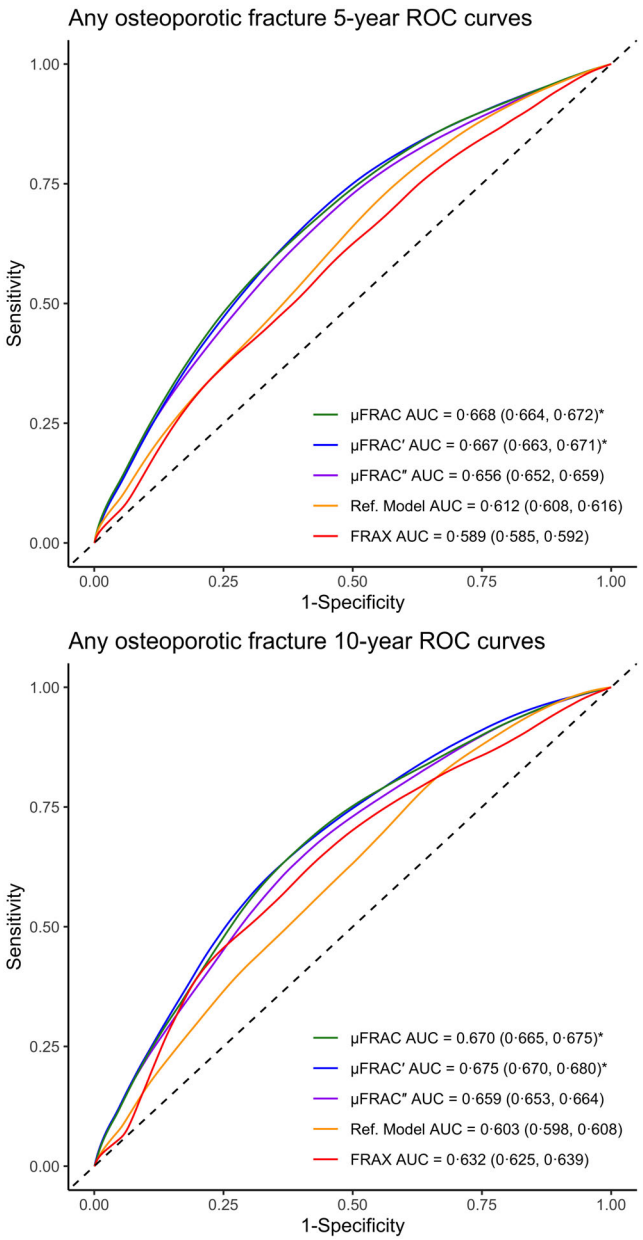

Fig. 3. Time-dependent receiver operator characteristic (ROC) curves for prediction of any osteoporotic fracture risk by μFRAC, FRAX, and the reference model built using femoral neck areal bone mineral density, sex, age, height, weight, and previous fracture as input parameters. The dashed line represents an area under the curve (AUC) of 0.50. *All models were significantly different ($p < 0.05$) from one another after post hoc comparisons except for μFRAC and μFRAC′ ($p > 0.68$).

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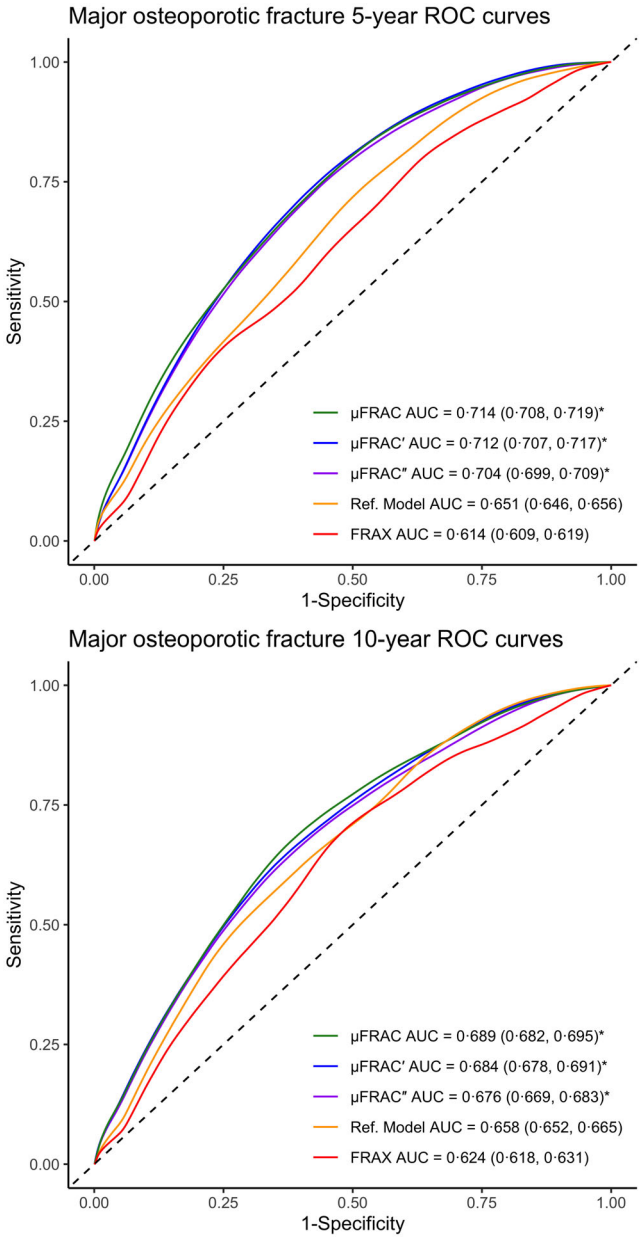

Fig. 4. Time-dependent receiver operator characteristic (ROC) curves for prediction of major osteoporotic fracture risk by μFRAC, FRAX, and the reference model built using femoral neck areal bone mineral density, sex, age, height, weight, and previous fracture as input parameters. The dashed line represents an area under the curve (AUC) of 0.50. *All models were significantly different ($p < 0.05$) from one another after post hoc comparisons except for μFRAC, μFRAC′, and μFRAC″ ($p > 0.05$).

The predicted μFRAC 5-year risk of any osteoporotic fracture ranged between 1.3% and 26.6% in males and 0.1%–35.0% in females. In both sexes the μFRAC score increases with age, with a steeper increase in women (Fig. 1). Comparison of the parameter VIMP ranking in the complete μFRAC model (Fig. 2) revealed that age and weight were the only clinical risk factors to rank above the model mean VIMP (0.012), whereas previous adulthood fracture had a near zero score. Evaluation of VIMP also revealed that the top predictors were measurements from a combination of skeletal sites (femoral neck, radius, and tibia), highlighting the model is capturing systemic skeletal frailty when determining an individual's fracture risk. When comparing VIMP scores across the simplified μFRAC′ and μFRAC″ models (Fig. 2), the VIMP of moderately ranked HR-pQCT parameters increased when FN aBMD and failure loads were removed, indicating these parameters are supplementing the information lost when these high-ranking predictors are removed.

The μFRAC models significantly outperformed FRAX and the reference aBMD model in predicting any osteoporotic fracture (Table 2). The complete μFRAC model had an overall c-index of 0.673, whereas simplified μFRAC′ and μFRAC″ models had slightly reduced performance (c-index = 0.668 and 0.659, respectively), but still modestly outperformed FRAX and the reference aBMD model (c-index = 0.636 and 0.617, respectively, $p < 0.001$). The time-dependent AUCs also showed that μFRAC was the top predictor of 5-year and 10-year risk of any osteoporotic fracture (Fig. 3). The margin of improvement obtained by μFRAC over FRAX in predicting 5-year fracture risk was an increase of 0.079 in AUC, equivalent to a 13% improvement. In addition, removal of FN aBMD, clinical risk factors (except age), and estimated failure loads from μFE did not significantly reduce performance ($p = 0.68$).

Results were consistent when only incident MOFs were considered, and predictive performance of all models improved compared with performance in predicting risk of all osteoporotic fractures. The μFRAC model was the best predictor of MOF (c-index = 0.733, $p < 0.001$), and only a marginal decrease in performance was observed in the simplified μFRAC′ and μFRAC″ models (Table 2, $p < 0.001$). The time-dependent AUCs for MOF risk showed that μFRAC provided improved prediction of 5-year and 10-year MOF risk over reference models (Fig. 4). The 5-year and 10-year AUCs obtained by μFRAC for MOF risk did not change significantly for the simplified μFRAC′ model where FN aBMD and clinical risk factors were removed ($p = 0.99$) or additional removal of μFE-estimated failure load in for the μFRAC″ model ($p = 0.06$).

Discussion

We developed a new fracture risk assessment tool, μFRAC, using a large international prospective HR-pQCT cohort. The model provides a 5-year and 10-year probability of any osteoporotic fracture and MOF. These outputs provide a clinically relevant approach to interpreting HR-pQCT patient data for estimating fragility fracture risk. Two alternative versions of μFRAC with fewer input parameters to reduce complexity for data collection resulted in only a modest reduction in predictive performance. The μFRAC tool modestly outperformed FRAX and a reference aBMD model when tested using bootstrap validation, highlighting the potential for μFRAC as a reasonable alternative to current clinical methods for assessing fragility fracture risk. The μFRAC tool provides comparable performance with existing fracture risk assessment strategies but takes a unique approach for assessing fracture risk. Fracture risk estimated by μFRAC is based on three-dimensional bone morphology measures, in lieu of clinical risk factors, an attribute that may be beneficial for secondary screening, or application in populations where DXA or FRAX are not well-suited.

Although machine learning approaches are often perceived as less interpretable than traditional methods, the basis of

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random survival forests is an ensemble of decision trees, an intuitive classification process similar to clinical decision-making methodology. The improved model interpretability may come at the trade-off of potentially reduced performance when compared to more advanced machine learning techniques, such as neural networks.[24] However, similar applications comparing machine learning techniques for survival-based statistics have found that the improvement gained with neural-net based methods is marginal when applied to imbalanced datasets,[49] thus providing little justification to adopt a more complex machine learning model in the context of this study design. Assessment of parameter VIMP that is generated by the random survival forest approach provides helpful insight into which parameters are most often used in the decision trees that are constructed, allowing the user to interpret how the machine learning approach determines fracture risk. The complete μFRAC model highlighted that FN aBMD, radius Tb.BMD, and estimated failure loads at the radius and tibia ranked higher than all other HR-pQCT parameters. These four parameters correspond directly to the phenotype-specific imaging biomarkers associated with fracture that were recently identified by our team.[50] Specifically, low FN aBMD and Tb.BMD are associated with higher fracture risk in the *low density phenotype*, whereas low failure loads at the radius and tibia are associated with higher fracture risk in the *low volume phenotype*. This suggests the random survival forest approach can identify the complex combinations of bone characteristics that define bone phenotypes in the population, and subsequently utilizes the appropriate imaging biomarkers to assess fracture risk.

Evaluation of VIMP scores is insightful, but it should be interpreted with caution. Although FN aBMD was a top predictor in the μFRAC model, it does not necessarily mean it is essential, as shown by the simplified μFRAC′ model. Removal of FN aBMD is possible because other density-based parameters, such as Tb.BMD and Ct.BMD, are highly correlated with FN aBMD, and consequently can substitute for FN aBMD if it is removed from the model. Similarly, when the failure load metrics were removed, the machine learning approach leveraged the other parameters provided to identify the complex combinations of bone properties that determine overall bone strength with only a marginal decrease in predictive performance. VIMP also revealed the low predictive ability of prior fracture, height, and sex in the μFRAC model. Although these characteristics have significant associations with fracture risk, the mechanism of this association is most likely through their relationship with bone strength,[10] so it is not surprising that they did not contribute to predictive modeling when direct measurement of bone characteristics are available. This indirect relationship of clinical risk factors to fracture risk is highlighted by the observation that 5-year and 10-years estimates of fracture risks did not differ by a significant margin when clinical risk factors, except age, were removed.

A unique aspect of μFRAC is the direct use of bone characteristics to assess fracture risk, in contrast to other fracture risk assessment tools that utilize clinical risk factors, which indirectly assess bone quality (eg, previous fracture). Several clinical risk factors are limited due to subjective interpretation related to dose-dependent or time-dependent effects (eg, glucocorticoid or smoking history), reliance on patient recall, or incomplete medical records.[5] In addition, well-established tools such as FRAX are not comprehensive; multiple clinical risk factors known to be associated with bone strength and fracture are not included (eg, physical activity), and validation has been performed using only treatment-naïve patients.[12] Consequently, because these tools rely on measures that indirectly infer bone strength, they would not be expected to account for considerations such as dose-dependent effects and pharmacologic intervention, and may misrepresent true fracture risk. A distinct advantage of HR-pQCT is that it is capable of detecting changes in bone characteristics following pharmacologic treatment,[51] even when changes are not yet detectable by DXA-based aBMD.[52] Because μFRAC estimates fracture risk directly from bone characteristics measured with HR-pQCT, it is likely that μFRAC can capture the impact of treatment on fracture risk that is not possible with other fracture risk assessment tools, or even FN aBMD. However, like many fracture risk assessment tools, μFRAC was not designed to capture an individual's fall risk. Nevertheless, the inclusion of age as a predictor in μFRAC offers a reasonable provisional surrogate for fall risk due its association with decreased physical function and declining health that leads to falls.[53] This may be why age was the only clinical risk factor in the complete μFRAC model that ranked highly in terms of variable importance; unlike other risk factors, age provided additive information beyond bone characteristics.

A limitation of this study is the use of internal bootstrap validation instead of an external validation. Although the BoMIC cohort captures a broad age range and geographic distribution (Europe and North America), the tool will require further validation with independent multiethnic cohorts in other geographic locations around the world. With this in mind, μFRAC will be made open access through an online platform (https://www.normative.ca/) for independent investigators to access, providing an opportunity for robust, unbiased external validation. Further, participants who were treated with an osteoporosis medication were not excluded from the population used to develop the models, unlike FRAX, which was developed with only treatment-naïve individuals.[17] We did not exclude participants who had osteoporosis treatment because inclusion is more reflective of real-world population demographics. A sensitivity test was performed to assess the effect of considering only treatment-naïve individuals in predicting MOF, and found that μFRAC, FRAX, and the aBMD reference models had incrementally reduced performance of 2.1%, 2.8%, and 1.3%, respectively, likely due to biased removal of individuals with more advanced osteoporosis (Table S5). Finally, the mean follow-up time of the population used to develop μFRAC was 4.7 years, which could explain why the 10-year estimate of fracture risk of μFRAC had reduced performance compared to the 5-year prediction. However, comparable to the populations used to model FRAX,[54] the mean follow-up of individual cohorts used to generate the BoMIC cohort ranges between 2.9–8.1 years,[22] allowing for reasonable estimation of 10-year fracture risk in line with FRAX.

Additional considerations when implementing μFRAC is that the prediction relies on data from the first-generation HR-pQCT scans obtained at both skeletal sites (radius and tibia). The use of load-bearing and non-load-bearing skeletal sites highlights that the model is basing the prediction on systemic bone health, but there are some cases when it is not possible to obtain sufficiently high-quality scans without motion artifacts at both skeletal sites. Further, the use of the second-generation HR-pQCT for developing the μFRAC model would be preferred as the research community shifts to the newer system, but large-scale prospective population studies needed to train the model are not yet available. Until sufficient second-generation data are available, cross-calibration methods can be implemented to allow for μFRAC to be used for individuals scanned using the second-generation HR-pQCT.[55] Another consideration with μFRAC is

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the accessibility of HR-pQCT systems for osteoporosis screening, limiting present-day utility of μFRAC to research-based cohorts and specialized clinics. Although significant progress has been made in development of HR-pQCT imaging over the past decade, technical and economic obstacles persist before HR-pQCT can be widely available.[56] Finally, μFRAC only provides estimates of overall osteoporotic fracture risk and MOF, but does not provide assessment of hip fracture risk, a primary osteoporotic fracture of concern. The BoMIC cohort had insufficient incident hip fracture events ($n = 50$) to develop a robust tool specific to this fracture site. However, exploratory investigation of the association between hip fracture risk and μFRAC 10-year and 5-year MOF scores indicate approximately 2-fold higher gradiaent of risk (hazard ratio per standard deviation increase) than scores obtained from FRAX 10-year MOF and FRAX 10-year hip fracture tools (Supplemental Table S6 and Supplemental Figure S1). Further, when the population was stratified by sex, only μFRAC was found to have a significant association with hip fracture risk in males (HR = 5.25, 95% CI: 3.17, 8.68), while FRAX 10-year hip fracture risk score had no significant association (HR = 1.44, 95% CI: 0.98, 2.12). Although the incidence of hip fractures in the BoMIC cohort is limited, these preliminary insights are in line with the gradients of risk estimated for all MOF relative to μFRAC and FRAX tools (Table S6 and Figure S1). Further investigation is required to ascertain the true performance of μFRAC in predicting hip fracture risk, and improvements to μFRAC could be realized by developing versions that rely on a single skeletal site (radius or tibia), and a version adapted for the second-generation HR-pQCT system.[56]

In summary, this study presents a novel tool to assess fracture risk using HR-pQCT and machine learning methods. The benefit of μFRAC is that it presents an alternative strategy from existing fracture risk assessment tools by leveraging direct measure of bone microarchitecture and density. Although HR-pQCT scanning is still relatively uncommon clinically, the μFRAC tool offers a new approach to interpreting HR-pQCT data for diagnosing and monitoring osteoporosis, accessible through an online tool and can eventually be incorporated directly into HR-pQCT systems for clinical implementation.

Author Contributions

Danielle E Whittier: Conceptualization; data curation; formal analysis; methodology; software; validation; visualization; writing – original draft; writing – review and editing. **Elizabeth J Samelson:** Conceptualization; data curation; funding acquisition; project administration; writing – review and editing. **Marian T Hannan:** Conceptualization; data curation; funding acquisition; project administration; writing – review and editing. **Lauren A Burt:** Data curation; investigation; writing – review and editing. **David A Hanley:** Data curation; investigation; writing – review and editing. **Emmanuel Biver:** Data curation; investigation; writing – review and editing. **Pawel Szulc:** Data curation; investigation; writing – review and editing. **Elisabeth Sornay-Rendu:** Data curation; investigation; writing – review and editing. **Blandine Merle:** Data curation; investigation; writing – review and editing. **Roland Chapurlat:** Data curation; investigation; writing – review and editing. **Eric Lespessailles:** Data curation; investigation; writing – review and editing. **Andy Kin On Wong:** Data curation; investigation; writing – review and editing. **David Goltzman:** Data curation; investigation; writing – review and editing. **Sundeep Khosla:** Data curation; investigation; writing – review and editing. **Serge Ferrari:** Data curation; investigation; writing – review and editing. **Mary L Bouxsein:** Conceptualization; data curation; funding acquisition; project administration; writing – review and editing. **Douglas P Kiel:** Conceptualization; data curation; funding acquisition; project administration; writing – review and editing. **Steven K Boyd:** Conceptualization; data curation; funding acquisition; investigation; project administration; resources; supervision; validation; writing – original draft; writing – review and editing.

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Peer Review

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Data Availability Statement

The population datasets analyzed during the current study are not publicly available to protect confidentiality and privacy of participants but may be made available from the corresponding author with reasonable justification and consent of co-authors bearing individual responsibility for their respective cohorts.

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