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PREDICTIVE VALIDITY OF RADIOGRAPHIC TRABECULAR BONE TEXTURE IN KNEE OA - THE OARSI / FNIH OA BIOMARKERS CONSORTIUM

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Jamie Collins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ROLE OF THE STUDY SPONSOR

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Abstract

Objective—To evaluate radiographic subchondral trabecular bone texture (TBT) as a predictor of clinically relevant osteoarthritis (OA) progression (combination of symptom and structure worsening).

Methods—The FNIH OA Biomarkers Consortium undertook a study of progressive knee OA cases (n=194 knees with both radiographic and pain progression over 24–48 months) and comparators (n=406 OA knees not meeting the case definition). TBT parameters were extracted from a medial subchondral tibial region of interest by fractal signature analysis of radiographs using a validated semi-automated software. Baseline TBT and time-integrated values over 12 and 24 months were evaluated for association with case and separately with radiographic and pain progression status adjusted for age, sex, BMI, race, baseline joint space width, WOMAC pain and pain medication use. C-statistics were generated from Receiver Operator Characteristic curves.

Results—Relative to comparators, cases were characterized by thinner vertical and thicker horizontal trabeculae. The summed composite of three TBT parameters at baseline and over 12 and 24 months best predicted case status (odds ratios 1.24–1.43). The C-statistic for predicting case status using the TBT composite score (0.633–0.649) was improved modestly but statistically significantly over the use of covariates alone (0.608). One TBT parameter, reflecting thickened horizontal trabeculae in cases, at baseline and over 12 and 24 months predicted risk of any progression (radiographic and/or pain progression).

Conclusions—Although associations are modest, TBT could be an attractive means of enriching OA trials for progressors as it can be generated from screening knee radiographs already standard in knee OA clinical trials.

Keywords

osteoarthritis progression; knee; trabecular bone texture; biomarkers; radiography

INTRODUCTION

Trabecular bone texture (TBT) is a way of representing the state of the vertical and horizontal trabeculae of a standardized region of interest of bone. Baseline TBT of the subchondral tibial bone in knee osteoarthritis (OA) cohorts has been shown to predict radiographic and/or magnetic resonance imaging (MRI) defined OA structural progression over the ensuing 12–48 months[1–3] as well as knee joint replacement[4] and incident OA[5]. TBT also changes concurrently with loss of joint space width (JSW), joint space area and MRI cartilage volume in knee OA progression[1, 2]. Notably, TBT has not been evaluated previously for its ability to predict pain progression or the combination of pain and structural progression.

TBT data are generated from a plain knee radiograph using a method known as fractal signature analysis based on prior work by Dr. C. Buckland-Wright[6] (and summarized

in[1]). TBT is a particularly attractive potential means of enriching OA trials for progressors as it can be generated from data extracted from the types of screening knee radiographs already standard in any knee OA clinical trial. In all fields, trial enrichment markers significantly improve the chances for successful phase transitions, the probability that a drug candidate will advance into the next phase of development[7]. It is estimated that two in four phase III trials will fail without selection biomarkers vs. only one in four with biomarkers[7].

The reasons for the translational failure of anti-OA drugs are multifold; reasons include the poor relationship in individual patients between joint structural pathology (especially joint space narrowing (JSN) on radiographs) and symptomatic disease, the limited responsiveness of existing biomarkers[8], the recognition that OA is a complex disease with multiple phenotypes that may each require somewhat different approaches for optimizing treatment[9] and the phasic progression[10] that results in enrollment of low numbers of progressors in the absence of effective enrichment strategies. A secondary analysis of a failed phase III clinical trial of risedronate for knee OA demonstrated the potential utility of biomarkers[11]. Although risedronate failed to demonstrate superiority in attenuation of knee OA structural deterioration based on JSN in this trial, CTX-II decreased with risedronate therapy and urinary concentrations at 6 months correlated with radiologic progression at 24 months. TBT analyses in this trial demonstrated a dose dependent therapeutic drug effect characterized by retention of normal trabecular structure in JSN progressor knees[12]. Even a modest strategy of enriching a trial for OA progressors or reducing screen failure rates (i.e., Risedronate trials had a screen failure rate of 73%[13]) could have significant cost implications. Not surprisingly, a European League Against Rheumatism (EULAR) committee of OA researchers, clinicians and patients has listed identification of predictors of OA progression as a high research priority, especially where this might enable stratified interventions[14].

Except for knee alignment, meniscal pathology, bone marrow lesions, synovitis and frequent knee pain[15–18], there are currently few other validated alternatives for enriching OA trials for structural progressors. The MRI acquired data (related to the meniscus, bone marrow and synovium) are relatively costly and sometimes inaccessible. The inexpensive and readily accessible data traditionally relied upon to identify progressors, such as OA risk factors of age, sex and body mass index, have been shown to be poor predictors from a heterogenous population of OA patients[1, 19, 20].

The objective of our study was to investigate the ability of baseline and short-term (over 12–24 months) radiographic medial subchondral TBT to predict clinically relevant medial knee OA progression (combination of symptom and structural worsening) over 48M. We hypothesized that TBT could be a valuable adjunct for enriching OA clinical trials for clinically relevant progressor subjects, thereby providing a means of increasing study power and potentially reducing study costs or enhancing trial efficiency due to the need to enroll fewer trial participants.

PATIENTS AND METHODS

Study Design

The FNIH OA Biomarkers Consortium undertook a nested case-control study (194 cases and 406 OA comparators) of progressive knee OA within the Osteoarthritis Initiative (OAI), a unique longitudinal cohort with a publicly available repository of joint images, biospecimens and clinical data obtained at annual clinic visits[21]. Details of the study design have been previously published[21, 22]. In brief, eligible participants for the present study were those with at least one knee with a Kellgren-Lawrence grade (KLG) of 1–3 at baseline from central reading and availability at baseline and 24M of knee radiographs, knee magnetic resonance images (MRI), stored serum and urine specimens and clinical data. One index knee was selected for each participant. Participants were excluded based on knee or hip replacement between baseline and 24M and radiographic and pain progression by 12M follow-up. Knees were excluded that had lateral JSN grade ≥2 at baseline.

Radiography

Radiography of both knees was performed at all clinic visits using the same non-fluoroscopic fixed flexion protocol (SynaFlexor, Synarc, Newark, CA)[23]. Radiographs were assessed by central reading for KLG[24]. The minimum JSW in the medial femorotibial compartment was measured using automated software[25]. Knees were excluded for poor radiographic positioning (defined by baseline medial compartment rim distance >6.5mm or change in rim distance of >2.0mm from baseline to all follow-up timepoints) because such knees would make measurement of minimum JSW unreliable.

Definitions of radiographic and symptomatic progression

Radiographic progression was defined by loss in medial minimum JSW of ≥0.7 mm from baseline to 24, 36 or 48M. Knee pain was assessed using the Western Ontario McMasters (WOMAC) pain subscale[26]. Based upon an established minimum clinically important difference (MCID) for pain worsening[27], persistent pain progression was defined as a pain increase of ≥9 points at 2 or more timepoints (on a 0–100 normalized score) from the 24M to 60M pain assessment (60M timepoint assessed to verify pain persistence if pain worsening endpoint reached at 48M).

Two main outcome groups were defined: case knees (n=194) with clinically relevant (both radiographic and pain) progression; comparator OA knees lacking the combination of radiographic and pain progression (n=406). Comparator knees could be subsetted into 3 groups: radiographic but not pain progression (n=103); pain but not radiographic progression (n=103); and OA non-progressors (n=200) with neither radiographic nor pain progression in the index knee and no joint space loss or pain progression in the contralateral knee. For better covariate balance among the groups, the knees selected for the four groups were frequency matched, using KLG strata 1–3 and body mass index (BMI) strata <25, 25–27.5, 27.5–30, 30–35 and ≥35 kg/m^2.

Trabecular Bone Texture (TBT) determination

TBT data were extracted from the same non-fluoroscopic fixed flexion knee radiographs used for KLG and JSW determinations. Radiographic analyses were performed using a validated and commercially available semi-automated software (KneeAnalyzer by Optasia Medical). The software provides a complex data set of variables (fractal dimension and radius) from the medial tibial subchondral bone of the knee that can be used to plot fractal signature curves (Figure 1). The software uses a 'horizontal filter' (HF) to generate data on the vertical trabeculae and a 'vertical filter' (VF) to generate data on the horizontal trabeculae. Our novel data reduction method relies upon a global shape analysis of the fractal signature curves and enabled us to convert the very complex fractal signature data from the medial compartment of each knee radiograph into 6 TBT parameters: HF intercept, HF linear slope, HF quadratic slope, VF intercept, VF linear slope, and VF quadratic slope; these parameters are suitable for subsequent regression and receiver operator characteristic curve (ROC) analyses. Global shape analysis of the fractal signature curves used Mixed Models[28] (assuming an autoregressive error structure). The Empirical Best Linear Unbiased Estimate (EBLUP) was derived for the mode including the linear slope and quadratic polynomials of Radius. In slight contrast to our prior work, extraction of the TBT parameters for these analyses originated from the nadir (and center) of the fractal signature curves to reduce the correlation between the estimated parameters. The advantage of this refinement has been to create near orthogonal (non-overlapping, independent) TBT parameters more suitable for multivariable and combinatorial statistical modeling and allowing the researcher to assess which parameter relates most to the outcomes under study. The absolute values of the parameters are therefore not directly comparable to prior published work but their ability to be predictive of outcomes should be as good, and their potential use in combination, improved due to the reduction of multicollinearity. The interrater reliability of TBT is very high, as previously reported[1]. To minimize confusion, all results are reported with reference to the horizontal or vertical filter from which they were generated.

Statistical analysis

In total, 579, 551 and 569 radiographs of suitable quality for TBT analyses were available at baseline, 12M and 24M, respectively. TBT analyses were based on baseline data and time-integrated values (TIVs) over 12M (n=538) and 24M (N=554). The pre-specified **primary analyses** evaluated the ability of the 6 individual TBT parameters to predict case status (n=194 cases with both pain and radiographic joint space loss progression versus n=406 comparators that did not have both pain and radiographic progression). The four pre-specified **secondary analyses** compared the best (based on univariable modeling) TBT parameter (VF linear slope) by each type of progressor status. Method 1 compared subgroups with pain and joint space loss progression, pain only progression and joint space loss only progression to the non-progressor reference group; Method 2 compared all progressors (radiographic or pain) to the non-progressors (neither radiographic nor pain progression); Method 3 compared all radiographic progressors to radiographic non-progressors; Method 4 compared all pain progressors to pain non-progressors. The main analysis used **multivariable regression** with TBT parameters transposed to z values

(created by subtracting the value for a subject from the total group mean and dividing by the standard deviation) in order for 1 unit of change to be comparable across the parameters; thereby, z score=0 represents the sample mean. This strategy overcomes the challenge of comparing measures with different ranges. Analyses were adjusted for covariates that included age, sex, BMI, race, baseline radiographic joint space width, baseline knee pain and use of pain medications. The best composite TBT score was derived by combining the z-scores of the 3 TBT parameters predictive in univariable models; two of the TBT parameters that predicted case status (VF linear and quadratic slope) had negative z-scores therefore they were reverse coded (sign changed) before summing them with the VF intercept (for which positive z-scores predicted case status) to create a composite score. Receiver Operating Characteristic curve (C statistic) analysis was used to determine the predictive capability of the parameters; parameters were evaluated individually or as a composite of 3 parameters. In addition to baseline values, TBT parameters were expressed in terms of time-integrated-values (TIVs) over 12M and 24M from baseline; these measures are equivalent to the area under the curve defined by the individual values for the specific time interval.

RESULTS

The demographic characteristics of participants selected for these analyses are listed in Table 1. Bivariate analyses of baseline demographic characteristics showed that lower KLG (OR 0.37 (95% CI 0.21, 0.66), no pain medication use (OR 0.66 (95% CI 0.44, 1.01) and higher baseline pain (OR 0.98 (95% CI 0.97, 0.99) were associated with lower odds of being a case (combination progressor by 48M); other baseline characteristics were not associated with case status including baseline JSW, BMI, age, sex, and race. The mean (SD) and median baseline TBT parameters for cases and comparators are provided in Table 2 as z-scores, and in Supplementary Table 1 as non-transformed variables. Three of the 6 TBT parameters (HF intercept, HF quadratic slope, VF quadratic slope) were associated with one or more of the baseline covariates (Supplementary Table 2). With the exception of the correlation of HF quadratic slope with HF intercept, the baseline TBT parameters were generally correlated but not collinear (Pearson r values <0.8, Supplementary Table 3).

Primary analyses with TBT parameters

Relative to primary comparators, primary cases were characterized by higher HF and lower VF fractal dimensions (Figure 1) reflecting thinner (more complex) vertical trabeculae and thicker (less complex) horizontal trabeculae, respectively. Over 12M and 24M, HF intercept (positively) and VF linear slope (negatively) were both statistically significantly associated with case status; over 12M, VF quadratic slope (negatively) was also associated with case status (Table 2). The summed composite of these 3 TBT parameters (as z-scores with reverse coding of the two slope components) at baseline and over 12M and 24M predicted case status with odds ratios (ORs) ranging from 1.24 to 1.43 (Table 2). Using the composite score, the C-statistic for predicting case status improved modestly but statistically significantly (0.633 to 0.649) over the use of the covariates alone (0.608).

Secondary analyses with TBT parameters

The TBT parameters were further evaluated for their ability to predict individual group status at 48 months, namely any progression, joint space loss (radiographic) progression, or pain progression. In each instance, VF linear slope was the best single and statistically significant TBT predictor (negatively) for each type of progression status (Table 3). This TBT parameter best predicted pain progression with C-statistic reaching 0.654 based on VF linear slope over 24M.

DISCUSSION

These results represent the fourth major validation of TBT as a predictor of OA progression, determined radiographically[1, 3, 29], by MRI[29], and now in our analysis, by a combination of symptom and radiographic worsening. We noted that progressor cases were characterized, in accord with all prior analyses, by trabecular remodeling of both horizontal (thicker) and vertical (thinner and more complex) trabeculae of the affected knee medial tibial subchondral bone compartment. Prior work suggested that individuals at risk for progressive OA have baseline TBT characteristics that reflect stress shielding from thickened horizontal trabeculae, resulting in apparently thin vertical trabeculae due to their hypomineralization as a result of a high subchondral bone turnover state. Buckland-Wright, the first to apply TBT methodology to the study of OA, considered increased horizontal trabecular thickness to be representative of early OA that preceded later changes in vertical trabeculae[6]. Horizontal trabecular thickening is intuitively congruent with traditional observations associating radiographic subchondral sclerosis with OA and OA progression. In this cohort study, thickening of the horizontal trabeculae was the characteristic most predictive of risk of OA progression and consistent with the inclusion of subjects with early OA (12–13% KL1; all patients had to have a baseline joint space width ≥0.7 mm, regardless of baseline KL status; there were no KL4 subjects). Also, compatible with the observation by Buckland-Wright that changes in vertical trabeculae were indicative of later OA, our prior study[1], showing greater changes in the vertical trabecular structures, was skewed toward more severe knee OA at baseline with inclusion of 10% KL4 knees.

The VF linear slope was the most predictive of primary case status and predicted all types of progression, including radiographic only and pain only progression. In secondary analyses, the strongest odds were observed for TBT (VF linear slope) prediction of OA progression based on the combination of pain and structural worsening (OR 0.71). As shown by a recent systematic review, subchondral bone features have independent associations with structural progression, pain progression and joint replacement in peripheral OA, especially in the knee[30]. These data support the increasing acceptance of the role of bone in both disease and illness aspects of OA disease progression.

Although in primary analyses, no baseline single variable was associated with case status, the baseline composite score of 3 variables was significantly predictive of case status. Moreover, baseline TBT parameters showed the same trends as the significant TBT 12M and 24M TIVs and baseline VF linear slope predicted any progression (all radiographic and/or pain progressors vs non-progressors). Compared to baseline TBT, the greater predictive capability of 12M and 24M TIVs (more proximal to the 24–48M endpoint time frame) for

predicting case status, pain and structural progression, is consistent with TBT as an indicator of proximal events.

In contrast to prior studies, TBT parameters in our study were computed from the nadir of the fractal signature curves to generate parameters that more closely yielded non-overlapping, i.e. orthogonal, data. Using this new method, we were able for the first time to evaluate the utility of the TBT intercept parameters. Interestingly, in addition to VF linear and quadratic slope terms, the HF intercept contributed useful information to a composite of three TBT parameters for predicting primary case status.

There are several limitations of our study that are worth noting. For one, the method of extraction of TBT parameters from fractal signature curves was slightly different from past published studies so the TBT parameters are not directly comparable. Efforts to standardize methods would be desirable, otherwise comparability across studies will be an ongoing challenge. We did not include data for the lateral compartment because medial compartment dominant knee OA was a requirement for study inclusion. A recent report demonstrated that the inclusion of lateral compartment data in predictive models, although not as strong as medial compartment data, provided the best predictive model[3]. In addition, no effort was made in this first phase biomarker qualification study to control type I error. It was curious that higher baseline pain was associated with lower odds of being a case; this might mean that knees with higher pain levels at baseline were less likely to have met the minimal clinical important difference (MCID) for pain worsening. Finally, participants in the main study were excluded based on radiographic and pain progression during the first 12 months' follow-up in an attempt to identify prognostic biomarkers in contrast to correlative biomarkers changing concurrent with progression; however, these rapid progressors may be the subjects most likely to be identified by TBT so their exclusion could have lowered the apparent prognostic capability of this imaging biomarker.

The best predictive capability displayed by TBT parameters for primary case status in our study (C-statistic 0.654) was lower than in all previous studies. This may be because the comparators in our primary analysis included some non-composite (radiographic only and pain only) progressors. The confirmation of this possibility was not borne out by secondary analyses that compared different progressor groups suggesting that elimination of individuals with radiographic progression over the first 12 months of observation might better account for the differences in this and prior studies.

In summary, these results show that adding TBT to the currently used predictors will modestly increase the ability to predict knee OA progression. These results confirm previous studies and together suggest that baseline TBT might be used in an OA trial enrichment strategy as outlined in FDA guidance[31]. TBT could be especially attractive as a means of enriching OA trials for progressors as it can be generated from data extracted from the types of screening knee radiographs already standard in any knee OA clinical trial. Future work will evaluate various combinations of soluble biochemical and imaging biomarkers for the various ways of proceeding to advance OA-related biomarkers as drug development tools.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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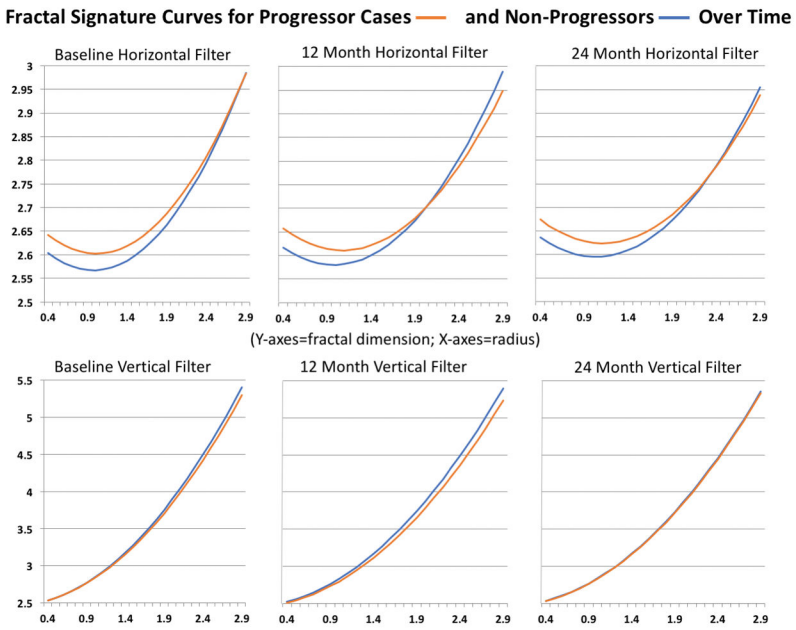

Figure 1. Graphic representation of fractal signature curves at baseline, 12M and 24M

Fractal signature curves are generated by plotting the fractal dimension (FD on the y axis) versus the radius (x axis). FD and radius generated from the horizontal filter of the KneeAnalyzer software yield information about the vertical trabeculae (panels A–C); curves derived from the vertical filter yield information about the horizontal trabeculae (panels D–F). The line graphs plot mean (raw unadjusted) data on subjects with observations at all 3 time points at baseline (panels A, D), 12 months (panels B, E) and 24 months (panels C, F). Orange lines depict the mean fractal signature curves for primary cases (knee osteoarthritis subjects with radiographic and pain progression from 24–48 months after baseline); blue lines depict the mean fractal signature curves for primary comparators (subjects with knee osteoarthritis but not meeting the primary case definition).

Table 1

Demographic characteristics of study participants (N=579).

Characteristic	Level	Comparators (n=394)	Cases (n=185)
Age, mean years (SD)		61.4 (8.9)	62.0 (8.9)
Sex, n (%)	Female	236 (60%)	108 (58%)
BMI, mean kg/m^2 (SD)		30.7 (4.8)	30.8 (4.8)
History of knee injury	yes	143 (36%)	65 (35%)
Baseline Knee Kellgren Lawrence (KL) Grade, n (%)	KL1	51 (13%)	22 (12%)
	KL2	218 (55%)	80 (43%)
	KL3	125 (32%)	83 (45%)
White Race	1	313 (79%)	146 (79%)
Baseline use of pain medication	yes	107 (27%)	62 (34%)
Baseline WOMAC pain score, mean (SD)		12.7 (16.5)	10.1 (12.8)
Baseline Joint Space Width, mean mm (SD)		3.9 (1.0)	3.8 (1.4)

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Table 2

Primary analyses based on baseline, 12M TIV and 24M TIV TBT parameter z-scores.

TBT Parameter	Cases Z score mean (SD) median	Comparators Z score mean (SD) median	OR (95% CI) (adjusted for covariates)	P value	C-statistic*
BASELINE: n=185 Cases (Group 1); n=394 Comparators (Groups 2–4)					
Intercept (HF)	0.12 (0.96) 0.39	−0.06 (1.01) 0.24	1.18 (0.98, 1.43)	0.0803	0.624
Linear Slope (HF)	0.05 (1.02) −0.05	−0.02 (0.99) −0.06	1.04 (0.87, 1.26)	0.6393	0.613
Quadratic Slope (HF)	−0.06 (0.92) −0.25	0.03 (1.04) −0.29	0.90 (0.74, 1.09)	0.2664	0.618
Intercept (VF)	0.06 (0.90) 0.09	−0.03 (1.04) 0.05	1.15 (0.95, 1.39)	0.1502	0.623
Linear Slope (VF)	−0.09 (1.07) −0.00	0.04 (0.96) 0.16	0.86 (0.72, 1.04)	0.1162	0.628
Quadratic Slope (VF)	−0.08 (0.92) −0.09	0.04 (1.03) −0.10	0.84 (0.69, 1.01)	0.0688	0.631
12M TIV: n=167 Cases (Group 1); n=371 Comparators (Groups 2–4)					
Intercept (HF)	0.15 (0.97) 0.41	−0.07 (1.01) 0.27	**1.23 (1.01, 1.50)**	**0.0442**	**0.622**
Linear Slope (HF)	0.00 (1.01) 0.02	−0.00 (1.00) −0.05	0.98 (0.81, 1.19)	0.8392	0.603
Quadratic Slope (HF)	−0.10 (0.91) −0.21	0.04 (1.04) −0.23	0.85 (0.70, 1.05)	0.1259	0.617
Intercept (VF)	0.03 (1.06) 0.11	−0.01 (0.97) −0.01	1.10 (0.91, 1.32)	0.3380	0.609
Linear Slope (VF)	−0.15 (1.10) −0.09	0.07 (0.95) 0.19	**0.79 (0.65, 0.95)**	**0.0140**	**0.628**
Quadratic Slope (VF)	−0.09 (1.05) −0.21	0.04 (0.98) 0.02	**0.81 (0.67, 0.99)**	**0.0364**	**0.623**
24M TIV: n=174 Cases (Group 1); n=380 Comparators (Groups 2–4)					
Intercept (HF)	0.15 (0.96) 0.42	−0.07 (1.01) 0.26	**1.26 (1.03, 1.53)**	**0.0246**	**0.628**
Linear Slope (HF)	−0.09 (0.93) −0.08	0.04 (1.03) −0.01	0.85 (0.70, 1.03)	0.0995	0.617
Quadratic Slope (HF)	−0.09 (0.89) −0.23	0.04 (1.05) −0.21	0.84 (0.69, 1.03)	0.0901	0.621
Intercept (VF)	0.02 (1.09) 0.09	−0.01 (0.96) 0.02	1.08 (0.90, 1.30)	0.4039	0.611
Linear Slope (VF)	−0.13 (1.09) −0.14	0.06 (0.95) 0.18	**0.80 (0.66, 0.97)**	**0.0227**	**0.631**
Quadratic Slope (VF)	−0.06 (1.03) −0.21	0.03 (0.98) −0.02	0.86 (0.71, 1.04)	0.1107	0.619
Composite TBT scores as predictors at baseline and over 12M and 24M					
Baseline Composite Score (3 parameters)	sum of HF intercept, VF slope, and VF quadratic term (vertical parameters reverse coded)		**1.24 (1.03, 1.49)**	**0.0223**	**0.635**
12M TIV Composite Score (3 parameters)			**1.32 (1.09, 1.60)**	**0.0047**	**0.633**

TBT Parameter	Cases Z score mean (SD) median	Comparators Z score mean (SD) median	OR (95% CI) (adjusted for covariates)	P value	C-statistic*
24M TIV Composite Score (3 parameters)			**1.43 (1.18, 1.73)**	**0.0003**	**0.649**

Primary analysis Cases: Knees with radiographic and pain progression from 24 to 48 months (Group 1), Comparators: Knees not meeting Case criteria (Groups 2–4).

Covariates adjusted for were baseline parameters including joint space width (JSW), WOMAC Pain, age, sex, race, BMI, Kellgren-Lawrence grade and baseline pain medication use.

*C-statistic adjusted for covariates. C-statistic for model with covariates alone 0.608

Data on vertical trabeculae derived from horizontal filter (HF) data; Data on horizontal trabeculae derived from vertical filter (VF) data; TIV=time integrated concentration; TBT=trabecular bone texture

Table 3

Secondary analyses based on baseline, 12M TIV and 24M TIV Linear Slope (VF) TBT z-core.

TBT Parameter	Comparison	OR (95% CI)*	P value*	C statistic*
Method 1: 4-level group (combination Rad and pain NON-progressors are reference group)				
Baseline	Rad only progressor vs. non-progressor	0.86 (0.66, 1.12)		
	Pain only progressor vs. non-progressor	0.83 (0.65, 1.08)	0.1873	
	Rad + pain progressor vs. non-progressor	**0.79 (0.64, 0.98)**		
12M TIV	Rad only progressor vs. non-progressor	0.86 (0.65, 1.15)		
	Pain only progressor vs. non-progressor	0.80 (0.61, 1.05)	**0.0327**	
	Rad + pain progressor vs. non-progressor	**0.71 (0.56, 0.89)**		
24 M TIV	Rad only progressor vs. non-progressor	0.89 (0.68, 1.18)		
	Pain only progressor vs. non-progressor	0.79 (0.61, 1.04)	**0.0453**	
	Rad + pain progressor vs. non-progressor	**0.73 (0.58, 0.91)**		
Method 2: All progressors vs non-progressors				
Baseline	All Progressors (Rad and/or Pain) vs Non-Progressors	**0.82 (0.68, 0.99)**	**0.0368**	**0.602**
12M TIV		**0.77 (0.63, 0.94)**	**0.0100**	**0.605**
24 M TIV		**0.78 (0.64, 0.95)**	**0.0153**	**0.606**
Method 3: Rad only progressors vs Rad non-progressors				
Baseline	Rad Progressors vs. Rad Non-Progressors	0.86 (0.73, 1.03)	0.0965	0.624
12M TIV		**0.82 (0.68, 0.98)**	**0.0289**	**0.632**
24 M TIV		**0.84 (0.70, 1.01)**	**0.0619**	**0.623**
Method 4: Pain progressors vs pain non-progressors				
Baseline	Pain Progressors vs. Pain Non-Progressors	0.85 (0.71, 1.01)	0.0656	0.639
12M TIV		**0.78 (0.64, 0.94)**	**0.0083**	**0.652**
24 M TIV		**0.78 (0.64, 0.94)**	**0.0083**	**0.654**

*Adjusted for sex, race, and baseline KLG, JSW, WOMAC pain, BMI and pain medication use; C-statistic cannot be calculated for the multinomial outcomes of Model 1

TBT=trabecular bone texture; Rad=radiographic