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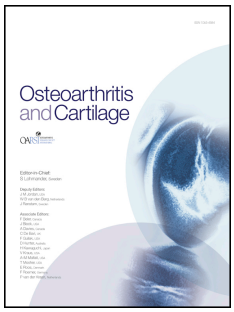

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[Tibial bone texture & knee OA progression]

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Abstract

Objectives: To examine whether trabecular bone texture (TBT) parameters assessed on computed radiographs could predict knee osteoarthritis (OA) progression.

Methods: This study was performed using data from the Osteoarthritis Initiative. 1647 knees in 1124 patients had bilateral fixed flexion radiographs acquired 48 months apart. Images were semi-automatically segmented to extract a patchwork of regions of interest (ROI). A fractal texture analysis was performed using different methods. OA progression was defined as an increase in the joint space narrowing (JSN) over 48 months. The predictive ability of TBT was evaluated using logistic regression and receiver operating characteristic (ROC) curve. An optimization method for features selection was used to reduce the size of models and assess the impact of each ROI.

Results: Fractal dimensions were predictive of the JSN progression for each method tested with an area under the ROC curve (AUC) up to 0.71. Baseline JSN grade was not correlated with TBT parameters ($R < 0.21$) but had the same predictive capacity (AUC 0.71). The most predictive model included the clinical covariates (age,gender, body mass index), JSN and TBT parameters (AUC 0.77). From a statistical point of view we found higher differences in TBT parameters computed in medial ROI between progressors and non-progressors. However, the integration of TBT results from the whole patchwork including the lateral ROIs in the model provided the best predictive model.

Conclusions: Our findings indicate that TBT parameters assessed in different locations in the joint provided a good predictive ability to detect knee OA progression.

Keywords: fractal analysis, trabecular bone texture, knee osteoarthritis, subchondral bone, radiography

Introduction

Osteoarthritis (OA) is the most common form of arthritis and is now considered as a disease of the whole joint organ involving mainly the articular cartilage, subchondral bone and synovial membrane but also the menisci and ligaments [1]. Recent research developments in imaging options for OA showed that most of the studies in OA imaging focused on the knee [2,3]. Conventional radiography is the currently accepted standard for monitoring OA progression and the progressive loss of cartilage can be assessed by the reduction in the joint space width (JSW) of the medial tibiofemoral compartment [4]. JSW narrowing is considered as a valid surrogate for the thickness of the articular cartilage, the meniscal loss and extrusion, and is still the only imaging marker recommended by the Food and Drug Administration for structural disease progression in clinical trials [5]. There is some debate about the most relevant definition of radiographic progression [6,7] and more recently on the inadequacy of conventional radiography either for assessing eligibility purposes but also as an end point in OA disease-modifying OA drugs trials [8].

It has been underlined that the identification of particular phenotypes of OA including different profiles according to bone mineral density may lead to a better management of the patient [6,9]. In line with these findings a renewed interest for the characterization of the subchondral bone texture on X-ray radiographs has been developed [10]. Several ways of describing subchondral trabecular bone texture (TBT) roughness have been used such as dissimilarity [11,12], fractal dimension (FD) [13,14] or fractal signature (FS) [15–17]. Fractal analysis for the trabecular bone characterization of OA joints was introduced in the 1990's by Lynch et al. [16,18]. It is a popular method due to its robustness against common radiographic problems such as exposure or pixel size variations [18].

Previous work used subchondral TBT parameters to predict the knee OA progression [12,15,19] and more recently the incident radiographic OA[20]. However, most of them used small samples of knee OA patients from a single clinical site of investigations. Consequently, herein aim was to confirm the capacity of TBT parameters to discriminate patients with or without knee OA progression and to predict this progression using data from a large, multicenter and open access database. We also focused on the assessment of the best descriptors for TBT characterization and on the choice of the region of interest (ROI) in the subchondral bone.

Material & Methods

Patients

Data used in the preparation of this article were obtained from the Osteoarthritis Initiative (OAI) database [21], which is available for public access at http://www.oai.ucsf.edu/. This database contains bilateral fixed flexion knee radiographs of 4796 patients followed since 2008. It is a multi-center and multi-equipment study. To avoid any digitalization artifacts, only the computed radiographs (CR), identified from the DICOM headers, were considered. In order to separate the different populations, only the knees from patients for whom the assessment of Kellgren-Lawrence (KL) [22] and Osteoarthritis Research Society International (OARSI) [23] grades as well as their clinical covariates: age, gender and body mass index (BMI) were available online, have been included. From this subset, the knees with preexisting non-severe OA at baseline were included in this study (preexisting non-severe OA was defined by a KL grade $\in [2; 4[$ in order to focus on the non-doubtfully OA patients with a worsening potential). Radiographs that presented knees with material, misalignment, radiographic defects or poor quality as defined in [24] were removed during the segmentation process.

Finally, the subpopulation used in this work consisted of 1124 patients (624 women and 500 men) in whom 1647 knees were radiographed and graded for both KL and OARSI scales. Table 1 provides the characteristics of the subgroup used in the present study. Established radiographic tibiofemoral OA cases and controls were selected as shown in Figure 1.

Acquisition and grading

During 72 months, participants had annual bilateral posteroanterior fixed flexion knee radiographs using the fixed flexion standardized positioner SynaFlexer [25]. In the present study, only the baseline radiographs were used. Radiographs were provided as 16-bits DICOM files from which we extracted parameters such as the date of acquisition, the modality or the pixel spacing. The resolution was not standardized in the database, the pixel size was variable from 150 to 200 µm for CR. Details concerning the acquisition [24] and grading [26] protocols in the OAI study are available online.

OA grouping

In this population, patients with or without OA progression were selected using the following definition: OA progressors (cases) designate patients with an increased medial JSN grade over the 48 months; while OA non-progressors (controls) designate patients with a constant medial JSN grade from baseline to 48 months acquisition. Table 1 provides the demographic data and OARSI grades for the two subgroups identified.

Regions of interest

A semi-automatic method was used to extract the trabecular bone ROIs. This method computes a patchwork of 16 square ROIs mapping the whole joint trabecular area. First, a trained operator (T.J) marked the tibial spines and the lateral and medial extremities of the

tibia. Second, the algorithm approximated the tibial subchondral bone plate as the brightest path going through these anatomical markers. Third, this estimation was used to fit the tibial plate orientation and clamp our patchwork under the cortical plates. To avoid subchondral bone sclerosis, a vertical adjustment of the ROI position was performed as proposed in [13]. To prevent periarticular osteophytes and fibular head overlay, an offset equal to 10% of the knee width was applied to the horizontal positioning. The ROIs dimensions were proportional to the knee width defined as the distance between the outer tibial margins. This provided an average side length of 62 ± 7 pixels, which represents a square of 1 ± 0.1 cm side. Figure 2 illustrates the result of the mapping using a 4-by-7 square patchwork.

Texture analysis

Fractal analysis is a suitable method for radiographic texture analysis since its parameters are linked to the 3D microarchitecture of the trabecular bone as shown at the calcaneus and vertebrae [27–30]. It is also considered as robust to radiographic magnification and projection [18,31], and inhomogeneous contrast [18,27]. Many methods have been developed to compute the FD of a signal [32–35]. In this study we compared three methods used for the trabecular bone characterization, the common technique of the fractal signature analysis (FSA) [18], the Whittle estimator (WhE) [35,36] and a method based on the quadratic variations (VAR) [34] used in DXA imaging [37]. In the following we will use the H parameter, which is directly linked to the FD and the roughness of the signal. Each method is described briefly below; further details are presented in supplementary files:

FSA estimator (FSA) [18] is the most common technique to compute the FD particularly in OA research field. The principle is to dilate and erode the signal using different sizes of structuring elements (SE) and compute the log-ratio of the area between the dilated / eroded

signals, and the size of the structuring element. In other words, FSA computes the differences between an under and over estimation of the signal according to the scale of observation and extract the fractal dimension (which is linked to the roughness) from the log-log plot regression of the curve. In this work, we used a line shape SE (which size varies from 3 pixels to half the length of the ROI) to compute the H in different directions. The fractal parameter H was computed as the slope of the log-log curve.

Quadratic variations estimator (VAR) [38] is a roughness measurement based on the variations of the pixels intensity for a defined step. Similarly to the FSA method, H can be computed from the slope of the log-curve of the quadratic variations against the scale. In this work we used the approach of Istas & Lang [34], computing H as the slope at the origin.

Whittle estimator (WhE) [36] is a maximum likelihood estimator based on the approximation of the likelihood function of a fractal signal increments. The aim is to fit the characterized texture to a fractal model driven by a single parameter H. This estimator is the most accurate in term of bias and variance when applied to synthetic fractal images [36,39].

Anisotropy: As shown in [12,19], the tibial trabecular bone is an anisotropic material. To consider the anisotropy into our descriptors, each analysis was performed on each ROI in different directions $\theta = \{0°; 45°; 90°; 135°\}$ providing exact computation of the roughness parameters without any interpolation. The retained values used are the H parameters obtained for 0° and 90° orientations (H_0, H_{90}) and the averaged value (H_{mean}) for $H_{\theta=\{0°;45°;90°;135°\}}$.

Each method was implemented in C++/MATLAB and validated on synthetic fractal images before processing the TBT ROIs.

Statistical analysis

First, the clinical covariates were investigated using the non-parametric test of Mann-Whitney for the numerical data and the Chi-square test for the nominal data. Using the obtained values (Table 1), we adjusted the results for the TBT parameters (Figure 3) using an ANCOVA with the following linear model: $\text{Group} \sim \text{TBT} + \text{Gender} + \text{BMI}$. The associations between clinical covariates, KL and OARSI grades and TBT parameters were evaluated using Pearson's correlation for the age and the BMI and Spearman's correlation for the KL and medial JSN grades at baseline.

Second, the prediction was evaluated using a logistic regression with several models including the clinical covariates, the center, the medial JSN grade at baseline and the different TBT parameters – H_0, H_{90}, H_{mean} computed with the different methods – WhE, FSA, Var. A total of six models were trained:

1. Clinical covariates i.e: Age + Gender + BMI + Center
2. TBT using WhE + clinical covariates i.e: WhE + Age + Gender + BMI + Center
3. TBT using FSA + clinical covariates i.e: FSA + Age + Gender + BMI + Center
4. TBT using VAR + clinical covariates i.e: VAR + Age + Gender + BMI + Center
5. JSN grade + clinical covariates i.e: JSN + Age + Gender + BMI + Center
6. TBT using WhE + JSN grade + clinical covariates i.e: WhE + JSN + Age + Gender + BMI + Center

As there are 3 TBT parameters computed in 16 ROIs, this results in 48 descriptors for each method (WhE, FSA, Var). In order to evaluate the effect of such large models on the prediction results, we trained the different models in three different ways, all avoiding interactions between the variables:

- **Complete:** the models were evaluated including the 48 TBT descriptors

- **Partial:** TBT parameters were restricted to H_{90} in the subchondral strip (7 upper ROIs in Figure 2) leading to 7 TBT descriptors in order to show the role of the 'most significantly affected part of the bone'.
- **Optimized:** a backward selection of the variables in the full models was automatically performed using the Akaike Information Criterion (AIC) as iterative criteria, resulting in 7, 10 and 15 TBT markers for WhE, VAR and FSA methods respectively. This AIC penalizes the complex models limiting the overfitting. The algorithm evaluates the AIC when removing iteratively each parameter and preserves the most efficient model.

For each model/method a 10-fold cross-validation was repeated 300 times to build the receiver operating characteristic (ROC) curves. The area under the curve (AUC) was used as a performance criterion. The comparison between the models was based on the ROC curves using the DeLong method [40].

All statistical analyses were performed using R (https://www.r-project.org) and the packages MASS (for the stepwise AIC optimization), Caret (for the cross-validation training) and pROC (for ROC curves and comparisons). Documentation for these packages is available online at https://cran.r-project.org/web/packages/.

Results

Clinical covariates

The clinical covariates are presented in Table 1 where the *p-values* indicate the significance level of the separation between progressors and non-progressors for each parameter at baseline. First, it can be noticed that dependencies exist between the gender ($P < 0.001$) and BMI ($P = 0.002$) of the patients and the progression of their OA. No significant differences were found between ages in the two groups ($P = 0.9$). Although the OAI database

is multi-centric and multi-equipment, no significant center effect was observed on OA progression ($P = 0.5$). Baseline medial JSN grade was significantly different in the two groups ($P < 0.001$).

Texture Parameters

Figure 3 presents the *p-values* for each TBT descriptor adjusted for gender and BMI. Results differed according to ROIs and to the fractal analysis method.

Horizontal FD (0°) was not significantly different between progressors and non-progressors except for the FSA method in the medial extremities of the patchwork (see Figure 3).

Vertical FD (90°) was significantly higher in progressors compared to non-progressors in almost every medial ROI for the three methods tested. However, results were more consistent along the whole patchwork for the WhE method with a decreasing gradient from subchondral medial area to the lateral deeper trabecular bone (Figure 3). The VAR method provided almost the same results as the WhE with lower significant *p-values*. FSA was more discriminant between progressors and non progressors in the lower part of the patchwork.

Average FD (360°) analyses as illustrated in Figure 3, did not add much to the 90° and 0° results.

Associations of TBT parameters and patient characteristics

The correlations between the TBT parameters and the subjects characteristics were computed separately for all TBT parameters applied on each ROI. No significant correlations were found at baseline between TBT parameters and clinical covariates nor OARSI grades. The maximum value for the correlation coefficient *R* was found for the association between TBT and the gender with *R* -0.34 (-0.38 -0.30) 95% confidence interval (CI). Targeting the JSN, *R* ranged from 0 (-0.05 0.05) 95% CI to -0.21 (-0.25 -0.16) 95% CI.

OA progression prediction

Figure 4, Figure 5 and Figure 6 present the performances of the models tested.

Complete models including every couple (TBT-descriptor, ROI) showed similar results for each fractal analysis method (models 2, 3 and 4 are statistically not different from each other: $P > 0.5$). Each method provided significantly similar results to the model using the JSN grade (models 2, 3 and 4 are statistically similar to model 5: $P > 0.5$). The combination of TBT parameters and the medial JSN grade in model 6 provided the best predictive model with an AUC of 0.76 which is significantly different from the other models (models 1, 2, 3, 4 and 5 were all statistically different from model 6: $P < 0.001$).

Partial models showed different results than the complete ones. The FSA model was no longer equal to the WhE and VAR models (models 2 and 4 are statistically different from model 3: $P < 0.001$) and can be assimilated to the model with only the clinical covariates (model 3 is not statistically different from model 1: $P > 0.1$). The best predictive model remained model 6 with an AUC of 0.73, still significantly higher than the other models ($P< 0.001$).

AIC optimized models provided the same results as the complete ones for the individual models 2, 3, 4 and 5, blurring the differences between the fractal analysis methods. Differences between models 2, 3 and 4 were improved but not significantly ($P > 0.3$). Model 6 remained the best model with an AUC of 0.74 and a significant difference compared to the other models ($P < 0.001$).

Discussion

In the present study, we have shown in the large sample of the OAI database that tibial TBT fractal parameters were predictive of the JSN in the medial compartment over 48 months

in patients with prevalent OA. The three different fractal analysis methods (WhE, FSA and VAR) provided consistent results in their capacity to predict OA progression. In line with our data, previous works have already highlighted the interest of the TBT parameters to separate OA progressors from non progressors [12,15,19].

Messent et al. [19] assessed over 24 months the changes in the subchondral and subarticular trabecular bone for 40 patients with medial compartment knee OA at baseline. They tested the ability of the FSA method to distinguish between the progressors and non-progressors over 48 months. They found longitudinal FD decreases in both vertical and horizontal directions in all OA knees. This decrease was significantly greater in patients with JSN > 0.2mm/year.

Compared to the Messent, Kraus et al [15] added clinical covariates to the TBT parameters in order to build predictive models of OA progression. Over a larger dataset (138–vs–40 patients) and for a longer period (3–vs–2 years) they showed that the better model for this task included a combination of FSA, knee alignment and clinical covariates (AUC 0.79).

More recently, Woloszynski et al. [12] have investigated the ability of TBT parameters to predict OA progression over a 4-year period. The analysis was conducted on 105 subjects in whom longitudinal digitized knee radiographs were obtained. They have found that the highest prediction accuracy (AUC 0.77) was provided by a model including textural parameters from a medial subchondral ROI with adjustment for age, BMI and gender. They used different descriptors for the roughness, based on the Gaussian kernels decomposition and focused on the anisotropic property of the subchondral knee TBT.

Effect of the fractal analysis method

The consistency of our results for the prediction of OA using the three different fractal analysis methods (WhE, FSA and VAR) indicates that the employed algorithm might have a low effect on the prediction results. It would also explain the consistency between the results

of Woloszynski [12] and Kraus [15] who computed roughness parameters using two different methods. However, when focusing on the individual ROIs the methods tested in this work provided different discriminant values in the patchwork (in Figure 3). This result shows differences in terms of sensitivity between the approach and could be explained by the fact that the three methods (WhE, FSA and VAR) were applied to non-exact fractal textures as suggested by the findings in the calcaneus TBT [35].

Effect of the ROI selection

Although previous studies [12,15,19] have used a reduced number of fixed ROIs, we used a patchwork that covers the full proximal tibial bone inspired by [11,41]. The subchondral medial area provided more relevant ROIs to focus on. However, the lateral area provided some significant differences for both WhE and FSA approaches. The absence of statistically significant differences in the lateral ROIs should not be claimed to ignore this area of the bone. Furthermore, the automated pruning of predictive models confirmed that the lateral side also contains information that, despite their lower significant value for discrimination, improved the prediction (see red ROIs in Figure 3). The same conclusions can be drawn for the deeper layers of ROIs and not only those ROIs immediately above the subchondral bone plate. Past studies focused on the subchondral part of the bone ignoring deeper areas, however, WhE and FSA highlighted ROIs with significant differences up to 3 cm under the tibial plate.

These aforementioned observations may lead to the hypothesis that the remodeling process involved in the progression of OA is not limited in specific subregions of interest of either medial or lateral tibial subchondral bone areas. It would also implicated both subchondral cortical bone and subchondral trabecular bone located in deeper areas that might

intervene in the complex interactions and cross talks between cartilage and bone tissue in the model of knee OA progression.

Effect of the orientation

We used only the two main directions (horizontal and vertical) plus an average of the parameter computed every 45°. The estimation of the parameters along the two main loading axes in Figure 3 allowed us to show and confirm that the main changes appear in the vertical (compression) direction. The FD in OA progressors was higher along the vertical direction and lower in the horizontal compared to the control group.

As suggested in [15], our findings show that the increase of the roughness in the compression orientation in progressors reflects an increased complexity in the vertical trabeculae organization, such as a higher trabecular number and a higher gap between coarser trabeculae reflecting an erratic bone remodeling process. Conversely, the decrease in the horizontal FD in progressors and consequently the smoothing of the texture could be explained by a coarsening of the trabeculae.

Comparison to the JSN grade

Our findings demonstrated that the TBT parameters could predict knee OA progression with the same predictive capacity as the initial JSN grade. In our study, the baseline JSN grade was not correlated with the TBT parameters whatever the ROI, the algorithm or the orientation considered. This would indicate that TBT parameters and JSN capture different information about the global joint degradation status. This was further confirmed with the improvement of the AUC when using both TBT and JSN in the same model and by the stepwise optimization of the complete model that kept both the initial medial JSN grade and several TBT parameters. This result differs with Woloszynski [12] and Kraus [15] observations

where the initial JSN grade was not predictive of OA progression. The lack of the predictive value of baseline JSN in their studies might be explained by the proportion of the JSN grades at baseline as for both studies they included more patients with lower JSN grades (merely 90% of JSN < 2 in Woloszynski work's [17], and inclusion of KL = 1 with consequently lower JSN grades in Kraus works [15]). We could hypothesis that TBT parameters would be better indicators for early OA stages prediction while JSN would be a better marker of late OA progression stage.

Limitations and strengths

First, the JSN score used was only a discrete ordinal grade and it might be more accurate to use the continuous value of the JSW to check if the prediction of OA progression can be improved.

Second, the OA progression was defined as an increase of the medial JSN grade. This definition was used to compare our results to the aforementioned studies [12,15,19.] . It should therefore be interesting to examine if the influence of the initial grade of JSN and the speed of narrowing could be predicted by TBT parameters changes. It has been found by Woloszynski et al that late OA progression prediction by TBT analysis might be more accurate than early stages of OA progression [12].

Third, we only considered for analysis the set of digital radiographs. In the OAI study, due to the multicenter and multi-equipment nature of the study some patients had conventional radiographs digitized for a second time. Moreover, we performed a retrospective analysis of knee OA progression in the OAI database thus not including potential confounders that could only be controlled in a prospective study.

Our study has several important strengths. We used the large OAI database (more than 1000 patients) of knee images and assessed the potential of different TBT analyses for the

prediction of OA progression. In addition in this database, the X-ray devices had not been x-calibrated, neither the variations in the acquisition parameters had been taken into account nor the impact of the soft tissue in the x-ray absorption and diffusion. This can appear as a limitation, however, our models managed to predict the knee OA progression. To insure that the results were not the consequences of a center effect we investigated the associations between the centers and the progression. The lack of center effect underlines the robustness of our approach since we were able to predict knee OA progression whatever the center. We also adjusted for potential clinical risk factors for OA progression (e.g. age, gender, BMI and JSN grade) in order to identify risk factors for various patterns of knee OA progression over time. In addition, due to our cross validation statistical approach we were able to build conservative estimates in our predictive models

Summary

In summary, over 4 years of follow up our findings suggest that in addition to baseline JSN grade, TBT parameters predict knee OA progression on digital radiographs. TBT parameters analyses might contribute to monitor the OA progression. Furthermore it could be relevant to select subgroup of knee OA patients that might be enrolled in clinical trials aiming at the evaluation of potentially costly drugs (biotherapies) that target the progression of the disease.

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Author Contributions

All authors contributed to the conception and design of the study, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and approved the final version submitted. Dr Lespessailles takes responsibility for the integrity of the work as a whole, from inception to finished article.

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Conflict of interest

All authors state that they have no conflicts of interest.

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Illustrations & legends

Figure 1: Flowchart diagram illustrating the selection of study subjects from the OAI dataset (*n* is the number of patients and *k* the corresponding number of knee radiographs at baseline). From the OAI initial database, non-severe OA patients (2≤KL<4) with graded knees and baseline computed radiographs were included.

Table 1: Characteristics of the 1124 patients - 1647 knee radiographs included in the study. Gender and Center characteristics did not change for baseline and 48 month, *p-values* are the significance levels of separation between progressors and controls for the different characteristics at baseline.

Figure 2: Knee trabecular bone mapping using a semi-automatic algorithm for ROIs selection. Dots are the anatomical markers manually defined, the highlighted line is the estimated tibial edge and the squared patchwork defines the ROIs.

Figure 3: Obtained p-values for TBT parameters in progressors versus controls. Values indicated in each ROI are the p-values in scientific notation (i.e 5E-02 means 0.05), significant values are highlighted. Red rectangles represent the ROIs automatically selected by the AIC-based models optimization. The columns: WhE, FSA and VAR correspond to the different methods of analysis while the lines: 0°, 90° and 360° correspond to the different directions of analysis (horizontal, vertical and the mean value computed for each 45°).

Figure 4: ROC curves obtained for the OA progression prediction using a 10-folds cross validation repeated 300 times. The complete models include Age, Gender, BMI and the 3 TBT descriptors computed over all ROIs (48 TBT markers).

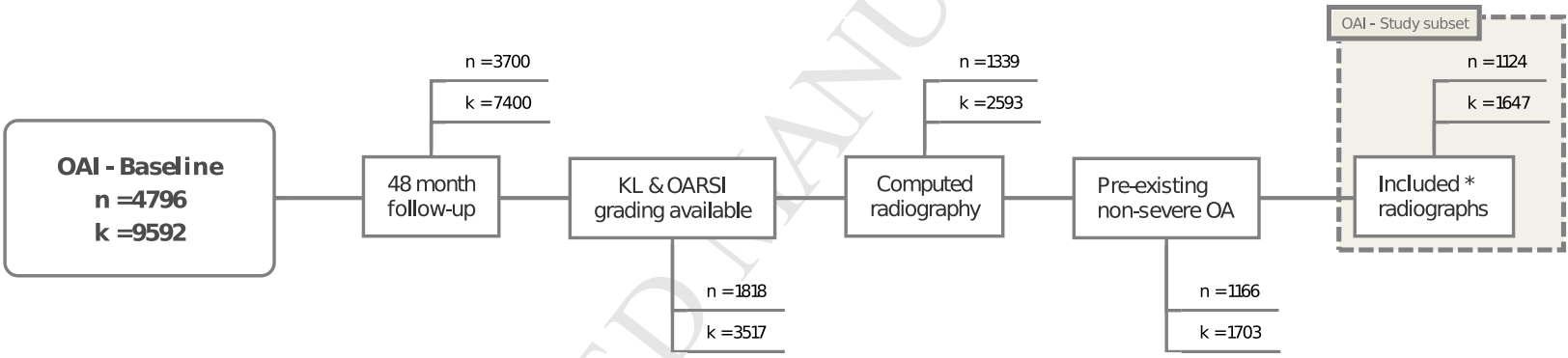
Figure 5: Obtained ROC curves for the OA progression prediction using a 10-folds cross validation repeated 300 times. The partial models includes Age, Gender, BMI and the TBT vertical descriptor computed over the 7 subchondral ROIs (7 TBT markers).

Figure 6: Obtained ROC curves for the OA progression prediction using a 10-folds cross validation repeated 300 times. The optimized models were built from the complete models using a stepwise backward selection minimizing the AUC.

	Baseline			48 Month			p-values
	Controls (k = 1419)	*Progressors (k = 228)*	*Total (k = 1647)*	*Controls (k = 1419)*	*Progressors (k = 228)*	*Total (k = 1647)*	
***Age** (years)*	62.7 ± 9.0	62.7 ± 8.2	62.7 ± 8.9	66.7 ± 9.0	66.7 ± 8.2	66.7± 8.9	0.995
***BMI** (Kg/m^2)*	29.3 ± 4.6	30.4 ± 4.6	29.5 ± 4.6	29.3 ± 4.8	30.7 ± 4.9	29.5 ± 4.8	0.002
***Gender** (no. knees)*							< 0.001
F	838	108	946	-	-	-	
M	581	120	701	-	-	-	
***Medial JSN grade** (no. Knees)*							< 0.001
0	620	31	651	620	0	620	
1	496	90	586	496	16	512	
2	303	107	410	303	128	431	
3	0	0	0	0	84	84	
***Center** (no. Knees)*							0.583
A	319	41	360	-	-	-	
C	580	92	672	-	-	-	
D	468	84	552	-	-	-	
E	52	11	63	-	-	-	

k: the number of knees

"-" means no changes compared to baseline



* Excluding radiographs with materials, poor positionning or acquisition artifacts