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SCIENTIFIC ARTICLE

Baseline knee joint effusion and medial femoral bone marrow edema, in addition to MRI-based T2 relaxation time and texture measurements of knee cartilage, can help predict incident total knee arthroplasty 4–7 years later: data from the Osteoarthritis Initiative

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Abstract

Objective To evaluate if baseline pathological knee conditions as assessed via single features of the MR-based Whole-Organ Magnetic Resonance Imaging Scoring (WORMS), standard T2, and T2 gray-level co-occurrence matrix (GLCM) texture parameters of knee cartilage can serve as potential long-term radiological predictors of incident total knee arthroplasty (TKA) 4–7 years later.

Materials and methods Baseline 3-T knee MRIs of 309 subjects from the Osteoarthritis Initiative ($n = 81$ TKA cases, with right-knee TKA 4–7 years after enrolment, and $n = 228$ TKA-free matched controls) were evaluated for the presence and severity of pathological knee conditions via modified WORMS. Knee cartilage was segmented and standard T2 cartilage and T2 GLCM texture measures (contrast, variance) were computed. Statistical analysis employed conditional logistic regression.

Results We found that a one-point increase on the joint effusion scale, the bone marrow edema scale or on the cartilage lesion scale at baseline predicted incident TKA (ORs: 2.45, 1.65, and 1.37 respectively ($p \leq 0.003$)). For T2 cartilage measurements, we observed that in the lateral femur, a 1-SD increase in T2 relaxation time yielded a 28% increase in the odds of TKA (1.28 [1.09–1.643], $p = 0.046$). When looking at cartilage texture, we similarly noted that a 1-SD increase in the cartilage texture parameter "contrast" was associated with a 33–40% increased risk of incident TKA in the lateral femur and tibia ($0.003 \leq p \leq 0.021$), as was a 1-SD increase in the texture parameter "variance" in the lateral femur ($p = 0.002$).

Conclusion Radiological evaluation of standard knee MR images via single WORMS features and T2 standard and texture analysis at baseline can help predict the patient's individual risk for an incident TKA 4–7 years later.

Keywords Cartilage T2 relaxation time · Magnetic resonance imaging · Knee · Total knee arthroplasty · Osteoarthritis · Predictive value of tests

Introduction

For about 700,000 patients in the USA annually, total knee arthroplasty (TKA) is the final common path of end-stage knee osteoarthritis (OA). By 2030, this number is projected to increase to 3.5 million annual TKA surgeries nationwide [1]. For many patients, TKA is beneficial and can help relieve pain, maintain and restore function, and improve the quality of life. Nevertheless, it carries surgery-related risks, including early prosthesis failure, infection [2] or deep vein thrombosis [3]. Particularly, long-term prosthesis failure is of crucial concern. With the expected rise in longevity and a current 10-year revision rate for TKAs of 6.2% [4], the number of revision TKA surgeries in the US alone is anticipated to increase drastically [1, 5]. Another shortcoming of TKA is its cost, which burdens the health care budget of countries with an aging population [6]. Therefore, current research strategies are focused on the prevention of the progression of knee OA to

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postpone the need for TKA as long as possible. However, prognostic markers that can identify patients at an early stage of knee OA who will be soon at risk for knee arthroplasty are scarce. Several studies have started examining the role of MRI in the prediction of knee arthroplasty [7–11]. However, all of these studies included only a small number of TKA cases [7, 8], had limited follow-up periods [11], were confined to subjects at a high risk for OA [10], or to low field strengths [12]. In addition, no study so far has investigated whether more advanced MRI-based techniques such as standard T2 relaxation time measurements [13] or T2-based gray-level co-occurrence matrix (GLCM) texture analyses [14], which provide detailed information about the composition and texture of knee cartilage, may be suitable long-term radiological markers for predicting TKA. Both methods have been shown to be sensitive to quantify early cartilage damage [15, 16] and therefore could potentially serve as early predictors of TKA when the course of the osteoarthritis might still be pharmaceutically or interventionally modified to delay TKA.

As severe debilitating joint pain is considered one of the most common causes for TKA in the clinical setting, we did not want to limit our study to assess the predictive abilities of cartilage alone, a knee joint structure that lacks innervation per se [17]. We were rather interested in evaluating the long-term predictive abilities of all other knee structures that have been shown to contain pain receptors (nociceptors) [17] and whose alterations have been found to be associated with increased pain levels [18–20]. Therefore, we aimed in this study to investigate in a large dataset from the Osteoarthritis Initiative whether knee structural damage, as assessed semi-quantitatively using single features of the modified MR-based Whole-Organ Magnetic Resonance Imaging Scoring (WORMS), standard T2, and texture measurements of knee cartilage at baseline can be used as long-term imaging predictors of incident TKA. We hypothesize that any of the three—baseline knee structural damage, standard cartilage T2 or texture measurements—can predict the incidence of TKA 4–7 years later.

Materials and methods

Subjects

Subjects for this nested case-control study were selected from the Osteoarthritis Initiative multi-center cohort study (OAI) as detailed in Fig. 1. The OAI was established to evaluate novel biomarkers, including novel imaging techniques such as T2 relaxation time measurements, for monitoring and predicting the onset and progression of knee osteoarthritis (http://www.oai.ucsf.edu/). The OAI has enrolled a total of 4,796 participants who are examined on a yearly basis at four clinical study sites across the USA. At each study visit, all participants are evaluated thoroughly via standardized questionnaires by trained personnel with respect to their health. The presence of osteoarthritis, pain, and osteoarthritis risk factors are assessed, along with a detailed medication history, assessment of other medical conditions, and history of surgeries. All patients also undergo a thorough physical examination and functional extremity testing. The clinical parameters/variables and images retrieved from these visits are coded and anonymized and are made available for research and free download online on the https://oai.epi-ucsf.org/datarelease website. At the time when our study was set up, adjudicated information on the presence of a past right knee total knee replacement (total knee arthroplasty = TKA) was available until the end of the 7th year of follow-up. Specific datasets utilized included baseline clinical dataset 0.2.2, baseline MRI dataset 0.E.1, and central radiograph reading datasets kXR_SQ_BU 0.5, 1.5, 3.4, 5.4, and 6.2. The OAI study is HIPAA-compliant and approved by the institutional review boards at each clinical site. All study participants signed informed consent forms before enrollment.

A total of 309 subjects were chosen from the OAI database based on the following inclusion and exclusion criteria (Fig. 1): subjects had to be aged between 45 and 79 years, had to have baseline MRI scans available, a BMI between 22.5 to 45 kg/m^2, and no history of rheumatoid or inflammatory arthritis. Only patients with Kellgren–Lawrence (KL) scores [21] of 0–3 at baseline were included, as patients with radiographic KL 4 grading do not have enough remaining knee cartilage to obtain T2 relaxation time measures. As we were interested in the long-term predictive abilities of WORMS, T2 and texture parameters, we only included patients in the TKA group (TKA cases) who underwent right knee TKA 4–7 years after enrolment into the OAI. TKA case selection was based on the OAI variable v99ERKTLPR in conjunction with the OAI variables v99ERKRPCF and v99ERKTPPR. The variable v99ERKTLPR codes for the question "Was this a total or partial replacement?" and is substantiated by the OAI variable v99ERKTPPR, which asks for the type of partial replacement and by the adjudication variable v99ERKRPCF, which asks if the knee replacement had been confirmed (either radiographically through visualization of X-rays or by surgical/medical documentation such as operative/discharge reports, or documented ICD codes). Control subjects had to be free of any self-reported or radiologically described TKA during the whole 7-year follow-up period. A final total of 84 cases fitted all inclusion and exclusion criteria. These 84 TKA cases were matched in a 1:3 ratio to TKA-free controls by gender (male/female), age (7-year strata from 45 to 79 years), BMI (in 10 kg/m^2 strata from 15 to 24.9 kg/m^2 and from 30 to 45 kg/m^2, and one stratum from 25 to 29.9 kg/m^2), race, and baseline KL scores (in strata of 0/1/2/3). Owing to missing baseline T2 images or insufficient image quality (see details below) a total of 81 TKA cases and

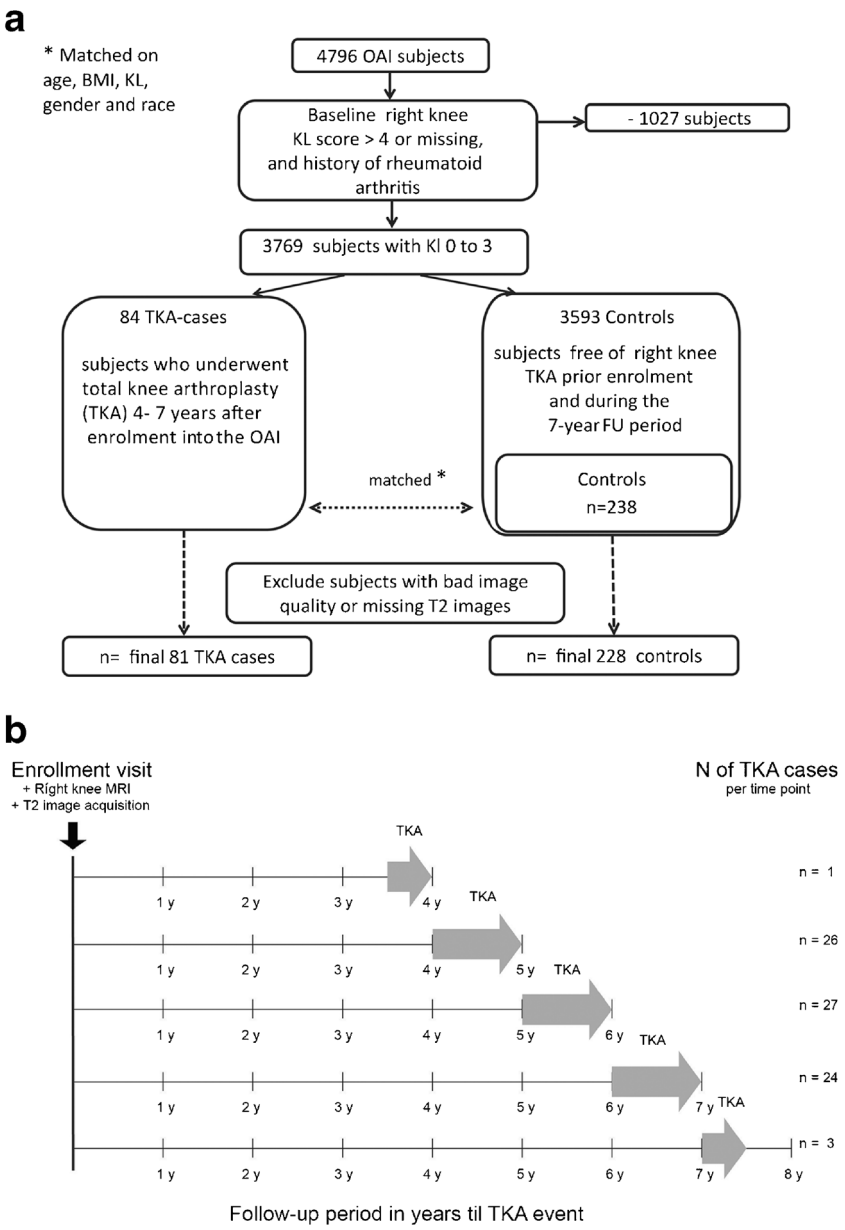

Fig. 1 **a** Flow chart depicting the selection process of total knee arthroplasty (*TKA*) cases and controls from the overall Osteoarthritis Initiative (*OAI*) dataset. **b** Overview of time intervals between enrollment visit and the date of TKA surgery in $n = 81$ TKA cases stratified by year of follow-up (*FU*). *KL* Kellgren–Lawrence score

228 controls were included in the final analysis. Out of these 81 TKA cases, 77 TKA cases underwent 4–7 years after enrollment an adjudicated right total knee arthroplasty. The remaining 4 TKA patients underwent within 4–7 years after enrollment a partial right knee replacement, which was specified in all 4 cases as a partial-medial replacement.

Imaging

KL scoring on radiographs

Standing bilateral posterior-anterior fixed-flexion knee radiographs were acquired at baseline using a standardized acquisition protocol across all sites, which is freely accessible online in the OAI X-ray operation manual under http://www.oai.epi.org. The radiographs were immediately reviewed for image quality on-site and were repeated until image quality met the quality criteria set by the OAI QA protocol. Knee films were graded for osteoarthritic severity at Boston University by an experienced musculoskeletal radiologist using the well-established Kellgren–Lawrence (KL) grading [21–23].

Magnetic resonance imaging

Right knee 3 Tesla MRI scans were obtained at baseline using a standardized OAI MRI imaging protocol [24]. All sequences were obtained at the 4 OAI clinical sites using identical 3 T MRI scanners (Siemens Magnetom Trio; Siemens, Erlangen, Germany) and standard transmit–receive knee coils (USA

Instruments, Aurora, OH, USA). A sagittal, two-dimensional, multislice, multiecho (MSME) sequence was acquired and used for T2 relaxation time quantifications (with TR = 2,700 ms; TE = 7; field-of-view = 12 cm; bandwidth = 250 Hz/pixel; in-plane spatial resolution = 0.313 mm × 0.446 mm; slice thickness = 3.0 mm; and gap = 0.5 mm). For WORMS readings [25] a coronal intermediate-weighted (IW) 2D fast spin-echo (FSE) sequence (TE/T2 29/3,700 ms), a sagittal 3D dual-echo in steady state (DESS) with selective water excitation (WE) (TE/TR 4.7/16.3 ms, flip angle 25°), and a sagittal 2D IW fat-suppressed FSE sequence (FS) (TE/TR 30/3,200 ms) were obtained and analyzed in all patients.

MR image analysis

(Modified) whole-organ magnetic imaging resonance scoring of knee structures

Baseline knee MR images were read by a blinded, board-certified musculoskeletal radiologist (JMW) with more than 6 years of experience in reading MRI examinations and 1 additional year of fellowship training in musculoskeletal radiology. The reading was performed after initial standardized training sessions, which included consensus training on knee pathology scorings with the chief musculoskeletal radiologist (23 years of experience; TML) [26]. All MR images were read for the presence and severity of pathological knee conditions using a semi-quantitative, modified version of the original WORMS grading system [25, 27]. This modified WORMS grading system has been employed in many previous publications [26, 28–31] including a recent study published in *Radiology* [32]. Compared with the original WORMS grading system, only 5 knee compartments in correspondence with the T2 compartments were analyzed [29, 30]. In brief, using the modified WORMS grading, meniscus morphology was scored on a severity scale of 0 to 4 in each of the six meniscal regions (anterior/body/posterior section of medial/lateral meniscus: 0 = normal meniscus morphology; 1 = intrasubstance abnormalities, 2 = nondisplaced meniscal tear, 3 = displaced or complex tear, and 4 = complete destruction). Cartilage lesions were graded in five compartments (patella, medial/lateral femur, and medial/lateral tibia) with the highest grade of lesion reported for each region, using the following eight-point scale: 0 = normal cartilage thickness and signal intensity, 1 = normal cartilage thickness or swelling with abnormal signal on fluid-sensitive sequences, 2 = single partial-thickness focal cartilage lesion <1 cm at its greatest width, 2.5 = single full-thickness focal cartilage lesion <1 cm at its greatest width. A cartilage score of 3 was given in the case of multiple areas of partial-thickness (grade 2) cartilage lesions intermixed with areas of normal cartilage thickness or a grade 2 cartilage lesion wider than 1 cm but encompassing <= 75% of the region. To get a cartilage score of 4, there had to be a diffuse partial-thickness cartilage loss spanning ≥75% of the region. For a cartilage score of 5, there had to be multiple areas of full-thickness cartilage loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm, but <75% of the region, whereas a score of 6 pertained to a diffuse, full-thickness cartilage loss involving more than 75% of the region. Another feature of the modified WORMS grading is the scoring of bone marrow edema (BME), which was carried out as follows: the presence of bone marrow edema (BME) was defined as any area of poorly marginated increases in T2 signal intensity in the fat-suppressed imaging sequences. A four-point rating scale was employed to assess the size of the bone marrow edema: 0 = no BME, 1 = minimal BME (diameter of <5 mm); 2 = moderate BME (diameter of 5–20 mm), 3 = severe BME (diameter of >20 mm). As part of the modified WORMS grading, the intactness and signal intensity of the cruciate and collateral ligaments, and of patellar and popliteal tendons were graded on a four-point scale (0 = normal; 1 = signal changes around the ligament; 2 = partial tear; 3 = complete tear). Joint effusion was scored via a four-point scale (0 = normal; 1 = <33% of maximum potential distension; 2 = 33–66% of maximum potential distension; 3 = >66% of maximum potential distension). The presence of a popliteal cyst, and the extent of subchondral cysts was evaluated as well. As the above explained single features of the modified WORMS grading are variables that provide knowledge of the presence of a single feature and of the extent of degeneration at a compartment-specific level, but do not provide information on a whole-knee level, cumulative sum scores were additionally computed as described before [32]. In detail, for each type of lesion (meniscus, cartilage, BME), a cumulative sum score per knee was calculated as the sum of scores in all five regions (patella, lateral/medial tibia and lateral/medial femur) [31]. These sum scores can be regarded as global knee parameters providing information at the global knee level that complements the single compartmental features. Additionally, for cartilage and for BME, a maximum damage score was defined as the highest score among the five knee joint compartments.

MRI knee cartilage segmentations

For T2 cartilage segmentation, a semi-automated spline-based segmentation was performed using a well-validated, in-house developed, MATLAB-based software (The Mathworks, Natick, MA, USA) [7, 30]. Five cartilage compartments (patella [PAT], medial [MF], and lateral femur [LF], and the medial [MT] and lateral tibia [LT]) were segmented on baseline MR sagittal 2D MSME sequences by two trained researchers (KD and JC) under the supervision of a radiologist (UH). Segmentations were performed such that each region of interest (ROI) enclosed the entirety of the cartilage tissue [31]. Segmentations were carried out on a slice-by-slice basis, ultimately spanning all slices containing the cartilage tissue.

Slices were excluded if the image quality was poor because of MRI artifacts or unclear delineation between the cartilage tissue and fluid, as described before [33, 34]. Using these criteria, three TKA cases and 10 controls could not be segmented, either because of missing baseline T2 images or insufficient image quality, leaving a total of 309 subjects (81 cases and 228 controls) for statistical analysis.

T2 relaxation time measurements

For all 309 subjects, T2 maps were generated from baseline sagittal 2D MSME images using a monoexponential decay model as a fitting function to calculate the signal intensity at each echo time [35]. T2 maps were computed on a pixel-by-pixel basis using a three parameter fit to account for noise. As omitting the first echo time (10 ms) optimizes the signal-to-noise ratio [36], T2 calculations were performed using the second (20 ms) to the last (70 ms) echo images (echo times = 20–70 ms) [36–38]. A global T2 value for the joint was computed by calculating the mean T2 values of all five compartments. Further information on the T2 methodology and analysis employed in our study can be also found in Wise et al. [34] in the article's supplement.

Gray-level co-occurrence matrix texture analysis

To receive more detailed information on the spatial distribution of T2 values within each knee cartilage compartment, we performed GLCM texture analysis of the knee cartilage on baseline sagittal 2D MSME images. The GLCM texture method is based on the algorithm by Haralick et al. [14, 39] and which measures the frequency of similarities in neighboring gray-level values occurring in an image. We selected two GLCM texture parameters as published by Carballido-Gamio et al. [40]: contrast, with high T2 contrast signifying great differences in neighboring T2 pixel values, and variance, analyzing the distribution of T2 pixels about the mean, with high values representing disorder in an image. Recent studies have found promising results that GLCM texture parameters can supplement compartmental standard T2 measurements by adding information at a pixel level and thus may allow for the detection of cartilage heterogeneity more efficiently [15, 40, 41].

Reproducibility

For each compartment and for all compartments combined, inter-reader reproducibility for T2 measurements was calculated on a percentage basis as the root mean square average of the single coefficients of variation, as published previously by Stehling et al. [42]. The inter-observer reproducibility error for mean T2 across all compartments was 1.57%, (0.53 ms). Mean intra-observer reproducibility for T2 measurements was 1.66% (0.55 ms). To estimate the amount of error in our semi-quantitative modified WORMS assessments, inter-reader agreement was determined in 20 randomly selected subjects as previously described [32]. The intraclass correlation coefficients (ICCs) for interobserver agreement were 0.88 (95% CI: 0.81, 0.94) for bone marrow edema [32], 0.918 (95% CI: 0.791, 0.967) for the bone marrow edema sum score, and 0.967 (95% CI:0.912, 0.987) for the bone marrow edema maximum score. For the meniscus, the ICCs for interobserver agreement were 0.996 (95% CI 0.990, 0.999) for the medial meniscus sum score, 0.991 (95% CI: 0.978, 0.997) for the lateral meniscus sum score, and 0.995 (95% CI: 0.887, 0.982) for the ligament sum score. The ICCs for cartilage lesion scores for interobserver agreement ranged between 0.874 (95% CI: 0.669–0.951) for the LT cartilage lesion score, up to 0.993 (95% CI: 0.982–0.997) for the MF cartilage lesion score. The lowest ICC with 0.777 (95% CI: 0.449–0.911) was found for the MT cartilage lesions score. The cartilage lesion sum score exhibited an ICC of 0.948 (95% CI: 0.871–0.979), whereas the cartilage maximum score showed an ICC of 0.971 (95% CI: 0.924–0.988). With respect to popliteal and subchondral cysts and joint effusion, the ICCs for interobserver agreement were 0.961 (95% CI: 0.903–0.985) for the popliteal cyst score, 0.852 (95% CI: 0.634–0.941 for the subchondral cyst sum score, and 0.860 (95% CI: 0.653–0.944) for the joint effusion score respectively.

Statistical analysis

Statistical analysis was carried out using SPSS 23 (SPSS, Chicago, IL, USA) and STATA version 13 (StataCorp, College Station, TX, USA). For intergroup comparisons of cases and controls, normal distribution of variables was first explored by visualization of histograms and Shapiro–Wilk tests. Conditional logistic regression models with adjustments for baseline Physical Activity Score of the Elderly (PASE) scores were employed for each WORMS feature, and for each compartmental T2 and texture parameter separately, in order to assess whether baseline WORMS features, T2 or texture parameters were associated with the occurrence of TKA. For T2 values, odds ratios (ORs) were reported as the percentage increase in the probability of TKR prevalence per 1-SD change in T2 value. For WORMS variables, ORs were calculated as the percentage increase in probability of TKR prevalence per one unit change. Statistical significance was defined as $p < 0.05$.

Results

Subject characteristics

Following the enrollment visit, 81 subjects (= TKA cases) underwent TKA. The time interval between enrollment visit and day of TKA varied among the 81 subjects (from a

minimum of 1,373 days to a maximum of 2,603 days after the enrollment visit) and it took on average 5.5 years (minimum 3.8 to maximum 7.1 years after the enrollment visit) until the TKA was sustained. Figure 1b breaks down the number of subjects per year of TKA. In detail, one subject underwent knee arthroplasty 87 days before the 4th year follow-up visit, a total of 26 patients received their arthroplasty between their 4th and 5th year of follow-up. Twenty-seven patients underwent knee arthroplasty between their 5th and 6th year of follow-up, 24 cases sustained their TKA between their 6th and 7th year of follow-up and a total of 3 patients underwent surgery for TKA within 48 days after the 7th year follow-up visit. Subjects in the TKA and control groups were similarly overweight (BMI 29 ± 4.6 kg/m^2), were on average 63 ± 8 years old, and exhibited similar proportions and similarly mild degrees of varus and valgus knee alignment at baseline and during follow-up (Table 1). Both groups showed a comparable racial and gender distribution (Table 1) at enrolment: in both groups, more than 85% of all participants were Caucasians, the majority (72.8%) of subjects were female, and exhibited either no to moderate osteoarthritis on Kellgren–Lawrence (KL) readings of their initial right knee radiographs. Furthermore, similarly high percentages of subjects in both groups (89–94%) complained of knee symptoms such as either knee pain, aching or stiffness over the last 12 months before enrolment. Other osteoarthritic risk factors were similarly frequent in each group: 42–44% of subjects per group reported a positive history of knee injury or knee surgery before enrolment; 38–45.7% showed Heberden nodes on their hands during the initial physical examination; and about 13–20% reported a positive family history for TKA. Patients in the TKA group showed a trend toward a higher (PASE) than non-TKA controls ($p = 0.050$) at baseline.

Presence and extent of structural pathological knee conditions at baseline assessed via modified WORMS

Upon assessment of the presence and severity of knee pathologies using the modified radiological WORMS system, we observed that both groups exhibited relatively low knee pathology scores: for most WORMS features such as the ligaments or the menisci, both groups ranked within mean scores between 0 and 2, indicating either no or limited damage/degeneration (Table 2). With respect to the extent and severity of baseline cartilage lesions, TKA patients exhibited an overall higher number and greater severity of knee cartilage defects relative to non-TKA controls in all compartments except the LF (MF $p = 0.000$, PAT $p = 0.011$, MT = 0.002, LT $p = 0.038$). The lateral femoral cartilage was the best preserved cartilage compartment with the lowest number and the lowest severity of cartilage lesions in both groups: more than 54% of TKA patients and more than 71% of controls were free from cartilage lesions in the LF (= WORMS cartilage grade 0; $p = 0.071$). The highest number and most severe cartilage lesions were observed in the patellar cartilage, where 76.5% of all TKA patients exhibited lesions of WORMS grade 3 or higher (18.5% grade 3 lesions, 11.1% grade 4 lesions, 32.1% grade 5 lesions, and 14.8% grade 6 WORMS lesions, $p = 0.011$). In addition, TKA patients displayed significantly larger extents of bone marrow edema (BME) and joint effusion (EF) in their baseline MRI scans relative to TKA-free controls.

Association of baseline knee structural damage as assessed via single features of WORMS with incident TKA 4–7 years later

We observed that several baseline knee pathologies were significantly associated with higher ORs of incident TKA 4–7 years later (Table 2). Of all baseline knee pathologies, the highest ORs for incident TKA were seen for joint effusion: an increase of one single point on the four-point joint effusion scale was associated with a 2.45 times higher OR for incident TKA 4–7 years later ($p = 0.003$). Moreover, a one-point worsening on the four-point bone marrow edema scale was associated with an up to 65% increased OR of later TKA: this association was found throughout all five bone marrow compartments, was most pronounced in the MF ($p < 0.001$), but did not reach statistical significance at the PAT. With respect to the presence and severity of cartilage defects, a one-unit increase in the WORMS cartilage lesion score was significantly associated with a 14–37% higher OR of undergoing a TKA (PAT: OR = 1.29 [1.10–1.50] $p = 0.001$; LF: OR = 1.19 [1.03–1.37] $p = 0.018$; LT: OR = 1.14 [1.00–1.31] $p = 0.057$; MF: OR = 1.37 [1.21–1.56] $p < 0.001$; MT: OR = 1.23 [1.09–1.38] $p = 0.001$). A one unit increase in the composite knee ligament score also yielded a significant 23% increase in OR ($p = 0.036$). Unit changes in baseline structural knee features such as meniscus or subchondral cyst extent showed a numerical, but not significant increase in OR for incident TKA 4–7 years later ($p > 0.05$).

Association of baseline standard cartilage T2 relaxation time measurements with incident TKA 4–7 years later

When looking at standard T2 relaxation time measurements by group, we observed that patients undergoing TKA exhibited numerically higher baseline mean T2 values compared with controls in all cartilage compartments; however, these differences did not translate into statistical intergroup significances ($p \geq 0.05$). But when we assessed the association of standard baseline mean T2 values by compartment with incident TKA, we observed that a 1-SD increase in the mean T2 relaxation time value in the lateral femoral compartment was

Table 1 Baseline descriptive characteristics of total knee arthroplasty (TKA) cases (= subjects with an adjudicated right knee TKA between 4 and 7 years after enrollment) and matched controls (= subjects free of any right knee TKA before and during the follow-up period of 7 years)

	TKA cases ($n = 81$)	Matched controls ($n = 228$)	p values TKA vs controls
Demographics and anthropometry			
Age (years)	63.3 ± 8.0	63.7 ± 8.1	0.228
Body mass index (kg/m^2) baseline	29.0 ± 4.5	29.4 ± 4.6	0.120
Body mass index (kg/m^2) after 2 years of FU	29.1 ± 4.7	29.4 ± 4.6	0.617
Body mass index (kg/m^2) after 4 years of FU	29.2 ± 4.7	29.2 ± 4.9	0.954
Body mass index (kg/m^2) after 6 years of follow-up	29.3 ± 4.9	29.2 ± 4.9	0.938
Gender, male (n %)	22 (27.2)	62 (27.2)	0.971
PASE score	169.3 ± 68.5	151.3 ± 78.5	*0.050*
Baseline Kellgren–Lawrence grade, n (%)			0.983
KL 0	2 (2.5)	6 (2.6)	
KL 1	4 (4.9)	10 (4.4)	
KL 2	40 (49.4)	117 (51.3)	
KL 3	41 (50.6)	111 (48.7)	
Racial composition			0.144
Caucasian, n (%)	70 (86.4)	204 (89.5)	
Asian, n (%)	1 (1.2)	0 (0.0)	
African–American, n (%)	8 (9.9)	23 (10.1)	
Non-Hispanic, n (%)	79 (97.5)	228 (100.0)	
OAI risk factors, n (%)			
History of knee injury[a], n (%)	34 (42.0)	100 (44.4)	0.701
Knee symptoms (either knee pain, aching or stiffness in the past 12 months before enrolment)	76 (93.8)	205 (89.9)	0.292
Family history of TKA	16 (19.8)	31 (13.7)	0.190
Heberden nodes present	37 (45.7)	86 (38.1)	0.229
History of knee surgery before enrollment	31 (38.1)	68 (30.0)	0.169
TKA status and TKA risk factors			
Time between enrollment and TKA (days)	2018.2 ± 325	n.a.	n.a.
Baseline alignment with goniometer of R knee			0.268
Varus alignment (%)	27.5	26.4	
Valgus alignment (%)	47.5	39.2	
Neither (%)	25.0	34.4	
Degree of varus alignment (°) ± SD	4.1 ± 2.5	4.1 ± 2.2	0.524
Degrees of valgus alignment (°) ± SD	−4.1 ± 1.9	−4.1 ± 2.2	
3-year alignment with goniometer of right knee			0.853
Varus alignment (%)	34.2	33.5	
Valgus alignment (%)	49.3	46.1	
Neither (%)	19.7	17.2	
Degree of varus alignment (°) ± SD	4.1 ± 2.1	3.4 ± 1.7	0.660
Degrees of valgus alignment (°) ± SD	−4.7 ± 2.8	−4.1 ± 2.6	

Data are expressed as unadjusted means ± SD

p values ($p < 0.05$) indicate significance

Borderline significances are printed in italics

KL Kellgren–Lawrence scores of radiographic osteoarthritis severity, *PASE* Physical Activity Score of the Elderly, *n.a.* not applicable

[a] Either knee so badly injured before enrollment that it was difficult for the patient to walk for at least 1 week

associated with a significant 28% increase in the OR of undergoing a subsequent TKA 4–7 years later (OR 1.28 [1.00–1.64], $p = 0.046$; Table 3). Figure 2 depicts two representative examples of T2 maps of the lateral femoral compartment, as found in a TKA case (Fig. 2a) and the matched control (Fig. 2b). For all other compartments, a 1-SD increase in the

Table 2 Overview of the presence and severity of baseline knee pathologies by group (TKA = subjects who underwent total knee arthroplasty 4–7 years after enrollment, controls = subjects who did not undergo any knee replacement surgery during the whole follow-up period of 4–7 years) as assessed on baseline 3 T knee MRI images using the modified semi-quantitative Whole Organic Magnetic Resonance Scoring (WORMS)

WORMS knee structures	TKA cases ($n = 81$)	Controls ($n = 228$)	Odds ratio (95% CI)	p value for odds ratios
Menisci and ligaments				
Medial meniscus sum score	1.59 (1.15–2.04)	1.31 (1.07–1.55)	1.07 ± (0.96–1.20)	0.224
Lateral meniscus sum score	0.93 (0.56–1.30)	0.77 (0.56–0.99)	1.05 ± (0.91–1.23)	0.490
Ligament score	0.69 (0.40–0.99)	0.38 (0.25–0.52)	1.23 ± (1.01–1.49)	*0.036*
Cartilage lesion score				
LF cartilage lesion score	1.28 (0.91–1.66)	0.82 (0.62–1.02)	1.19 ± (1.03–1.37)	*0.018*
LT cartilage lesion score	1.47 (1.08–1.86)	1.08 (0.86–1.30)	1.14 ± (1.00–1.31)	0.057
MF cartilage lesion score	2.96 (2.51–3.42)	1.77 (1.53–2.01)	1.37 ± (1.21–1.56)	*< 0.001*
MT cartilage lesions score	2.07 (1.61–2.54)	1.30 (1.06–1.54)	1.23 ± (1.09–1.38)	*0.001*
PAT cartilage lesions score	3.65 (3.22–4.08)	2.81 (2.55–3.06)	1.29 ± (1.10–1.50)	*0.001*
Cartilage lesion sum score	11.44 (10.3–12.62)	7.65 (7.01–8.21)	1.17 ± (1.11–1.23)	*< 0.001*
Cartilage maximal score	4.64 (4.36–4.93)	3.70 (3.49–3.92)	1.61 ± (1.27–2.06)	*< 0.001*
Other knee structures				
LF bone marrow edema score	0.35 (0.17–0.52)	0.20 (0.12–0.28)	1.38 ± (0.95–2.00)	0.090
LT bone marrow edema score	0.44 (0.26–0.63)	0.29 (0.20–0.39)	1.30 ± (0.93–1.83)	0.120
MF bone marrow edema score	0.78 (0.55–1.01)	0.38 (0.29–0.47)	1.65 ± (1.26–2.15)	*< 0.001*
MT bone marrow edema score	0.81 (0.57–1.05)	0.60 (0.48–0.73)	1.21 ± (1.00–1.49)	0.054
PAT bone marrow edema score	1.01 (0.79–1.23)	0.83 (0.70–0.95)	1.21 ± (0.93–1.57)	0.150
Bone marrow edema sum score	3.40 (2.82–3.97)	2.26 (2.01–2.51)	1.26 ± (1.13–1.39)	*< 0.001*
Bone marrow edema maximal score	1.80 (1.60–2.01)	1.45 (1.32–1.57)	1.44 ± (1.06–1.96)	*0.020*
Popliteal cyst score	0.81 (0.58–1.05)	0.72 (0.59–0.84)	1.11 ± (0.85–1.47)	0.429
Subchondral cyst sum score	2.04 (1.49–2.58)	1.70 (1.43–1.97)	1.08 ± (0.96–1.20)	0.207
Joint effusion score	0.27 (0.15–0.39)	0.09 (0.05–0.14)	2.45 ± (1.36–4.42)	*0.003*

Mean scores and 95% confidence intervals for each knee feature are given. In addition, the odds ratio for a later total knee replacement is given for each knee feature along with the 95% confidence interval

Statistical significance is assumed at $p < 0.05$

Significant p values are printed in italics

LF lateral femur, *LT* lateral tibia, *MF* medial femur, *MT* medial tibia, *PAT* patella

mean T2 relaxation time values was not significantly associated with an increased OR of an incident TKA.

Association of baseline GLCM texture-derived parameters with incident TKA 4–7 years later

As for cartilage GLCM texture parameters, we observed that in the LF a 1-SD increase in the T2 texture parameters "contrast" and "variance" were both significantly associated with incident TKA (LF contrast: OR: 1.40 [1.12–1.77], $p = 0.003$; LF variance: OR 1.41 [1.14–1.75], $p = 0.002$, Table 4). Likewise, we noted that in the LT a 1-SD increase in the T2 texture parameter "contrast" was related to a 33% increased OR of undergoing TKA within 4–7 years later (OR 1.33 [1.04–1.71], $p = 0.021$). Interestingly, with respect to the patellar cartilage texture, we found that a 1-SD increase in baseline patellar entropy and variance was associated with a 35–55% reduced OR of subsequent TKA respectively ($p \leq 0.009$).

Discussion

This study examined if knee structural damage as assessed via single features of the modified WORMS, via standard cartilage T2 relaxation time measures, and via texture T2 parameters at baseline can be used as early predictors of incident TKA 4–7 years later.

One of our main novel findings was that advanced MR-based cartilage imaging techniques, such as baseline standard T2 relaxation time measurements and GLCM texture analysis, can be associated with increased ORs of incident TKA 4–7 years later: knees with 1-SD increase in T2 relaxation time

Table 3 Baseline standard mean cartilage T2 relaxation time measurements ± SD in milliseconds presented by group and odds ratios of incident TKA 4–7 years later

Compartment	Mean T2 (in ms)		Odds ratio (95% CI)	*p* value for odds ratios
	TKA cases ($n = 81$)	Controls ($n = 228$)		
LF	36.66 ± 2.89	35.95 ± 3.23	1.28 (1.00–1.64)	*0.046*
LT	28.65 ± 2.87	28.61 ± 2.93	1.04 (0.81–1.34)	0.741
MF	39.95 ± 2.44	39.68 ± 3.25	1.12 (0.89–1.42)	0.325
MT	30.29 ± 2.94	29.81 ± 2.62	1.17 (0.90–1.55)	0.245
PAT	32.34 ± 3.18	32.78 ± 3.29	0.85 (0.64–1.12)	0.244
GLO	33.59 ± 1.97	33.36 ± 2.22	1.15 (0.92–1.45)	0.220

LF lateral femoral, *LT* lateral tibial, *MF* medial femoral, *MT* medial tibial, *PAT* patellar, *GLO* global knee (all compartments combined)

values in the lateral femoral cartilage compartment had about a 30% increased OR of undergoing knee replacement 4–7 years later. A One unit change in T2 values in all other cartilage compartments, in contrast, was not associated with higher odds of later TKA. This result seems at first glance surprising, as we would have expected standard T2 measurements to be predictive of incident TKA in all cartilage compartments. However, at a second glance, these findings can be explained by the technical limitations that are implicit in the T2 relaxation time methods: from previous studies we know that standard T2 relaxation time measurements work best when the cartilage is still well-preserved, and when adequate amounts of residual cartilage volume and thickness are still left so that segmentations can be performed [16]. In addition, for standard T2 measurements to work best, the amount and severity of cartilage lesions in the compartment of interest should be as low as possible because of the limited dynamic range of T2 values [43]. In our study, the lateral femoral compartment had the lowest amount and the lowest severity of cartilage lesions of all five compartments: more than 54% of TKA patients and more than 71% of controls were without any cartilage lesion in the LF (=WORMS grade 0), making it the least affected compartment. Our finding that baseline mean standard T2 of this least impacted LF cartilage compartment was significantly associated with a higher risk of later TKA is encouraging, as it shows that mean T2 may be a useful long-term predictor of TKA, particularly in less severe osteoarthritic cases where the cartilage is still mostly intact. Additional studies with ultra-long follow-up times (more than 7 years) are needed to fully elucidate the potential of standard T2 relaxation time measures as ultralong-term predictors of TKA.

When looking at the baseline GLCM T2 texture analysis, we also observed that a 1-SD increase in the T2 texture parameters "contrast" and "variance" was associated with incident TKA. In particular, in the LF, where the amount of cartilage lesions was mild, a 1-SD increase in contrast and variance texture T2 values was associated with an approximately 40% increased likelihood of undergoing TKA 4–7 years later. A similar association (33% risk) was observed in the LT, where the severity of the cartilage lesion was also mild and comparable between groups. Contrast and variance are parameters that capture the T2 intensity differences of directly neighboring T2 pixels within a cartilage compartment (contrast) and how orderly the cartilage architecture is preserved (variance) [40]. Our TKA cases showed consistently numerically increased contrast and variance measures in all compartments, except for the PAT. The increases were most pronounced and significant in the lateral femorotibial cartilage pointing toward a more disorganized and heterogeneous cartilage profile in this joint part with TKA cases. The reason the T2 texture measures may not have reached significance in the medial femorotibial joints may be owed to the fact that these medial compartments had a higher amount and severity of cartilage lesions. T2 GLCM texture analysis is a technical extension of the initial T2 standard analysis, it utilizes the initial standard T2 segmentation of interest and employs a pixel-based spatial subanalysis to this initial segmentation. Therefore, T2 GLCM texture analysis may underlie the same, above-mentioned cartilage specifications that are required for the standard T2 analysis to work best: an adequate volume and thickness of the cartilage of interest and a low amount and severity of the cartilage lesion. However, further studies are needed to confirm the exact dynamic range of T2 GLCM texture parameters.

Using single features of the radiological modified WORMS grading system, we found in line with previous small-sized [12] or short-term studies [11] that knees that exhibited a higher bone marrow edema pattern or a cartilage defect at the MF at baseline were at increased risk for knee replacement 4–7 years later, whereas knees with subchondral cysts had a much better prognosis. The fact that we observed the highest ORs for cartilage defects in the medial femoral compartment also resonates with the existing literature: using data from the OAI and different cartilage metrics, Eckstein and coauthors were able to demonstrate that cartilage thickness in the medial femorotibial compartment is reduced in knees with subsequent knee replacement 1–4 years later [44].

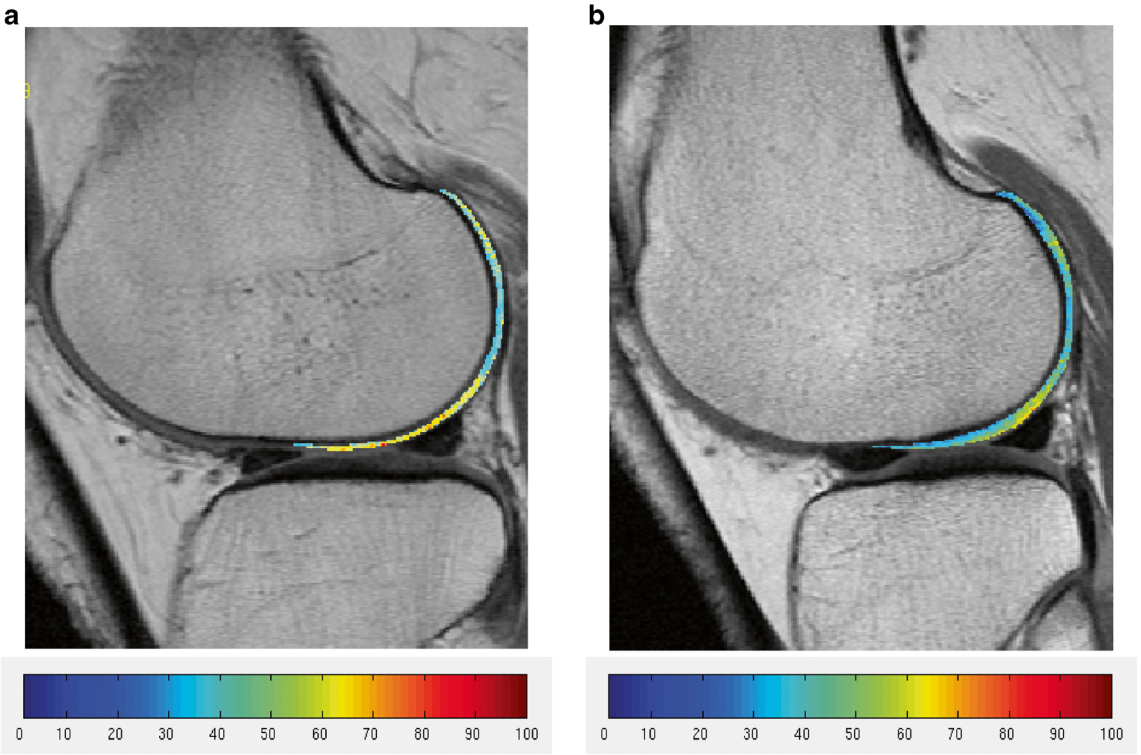

Fig. 2 Representative, color-coded, sagittal, baseline T2 maps showing the segmented lateral femoral cartilage of **a** a TKA case and of **b** the corresponding, matched control. Cartilage of the TKA case shows higher T2 values. Image **a** was acquired in a 75-year-old Caucasian woman with a BMI of 25 kg/m^2, who underwent right total knee arthroplasty about 4.3 years after initial enrollment into the OAI multicenter study. Image **b** stems from the corresponding matched control, who is also a 75-year-old Caucasian women with a BMI of 25 kg/m^2, but who did not undergo total knee arthroplasty

Another important finding of the radiological evaluation of baseline knee pathologies was that a one-point increase on the four-point joint effusion grading scale was associated with a 2.45 times higher OR for subsequent TKR 4–7 years later. These findings extend those of a previous ultrasound study reporting joint effusions larger than 4 mm as predictors of TKA 1–3 years later [45]. As a synovial effusion is regarded as one of the surrogate features of joint synovitis in unenhanced images [46], our results strengthen the proposed role of joint inflammation as an important osteoarthritis precursor and accelerator [47, 48].

Our study has several limitations. First, the follow-up time was limited to 4–7 years. To specifically evaluate standard T2 and texture parameters, longer follow-up periods would have been more advantageous. However, we included all the information that was accessible from the OAI when our study was set up. Future studies should try to investigate the predictive abilities of T2 in large cohorts with even longer follow-up times to TKA. In addition, we included patients with preexisting moderate OA (KL scores of 3) in our study to increase our sample of TKA cases. This may have been partly responsible for the lack in significances we observed for the standard T2 analysis which is supposed to work best in less diseased cartilage compartments [43]. Another drawback of our study is that we may have introduced some selection bias as we limited our study to MRIs of the right knee only. However, the sagittal 2D MESE sequence, which serves as the basis for our T2 relaxation time quantification, had been acquired owing to time restraints and per a priori decision of the OAI imaging working group [24] only at the right knee. Therefore, our potential selection bias was OAI-inherent and not avoidable because of the constraints of the MRI study protocol. Another limitation pertains to the approach to generating cumulative sum scores. Cumulative sum scores are helpful as they can provide information on the extent of degeneration/penetration of a single WORMS feature at the whole-knee level. Nevertheless, the effect of their compositional variance on clinical significance remains to be determined. Future studies need in particular to investigate whether, for example, a cartilage sum score of 6 that was composed through a single grade 6 lesion, has the same clinical significance as a cartilage sum score of 6 that was composed through six grade 1 cartilage lesions. A further limitation of our study is that we did not account for knee malalignment in our design or in our statistical analyses. However, preliminary analyses of the amount and degree of baseline varus and valgus deformities in our study revealed that approximately the same proportion of patients in both groups showed alignment deformities and that these deformities were in general mild. Another weakness of our study is that our T2 analyses were—apart

Table 4 Baseline gray-level co-occurrence matrix T2 (GLCM) texture analysis by knee compartment and group

Texture analysis	Mean T2		Odds ratio (95% CI)	*p* value odds ratio
	TKA cases ($n = 81$)	Controls ($n = 228$)		
Contrast				
LF	304.9 ± 81.0	278.7 ± 75.0	1.40 (1.12–1.77)	*0.003*
LT	202.9 ± 92.4	183.1 ± 60.0	1.33 (1.04–1.71)	*0.021*
MF	485.7 ± 153.3	458.4 ± 139.2	1.19 (0.94–1.50)	0.137
MT	340.1 ± 122.2	323.7 ± 111.3	1.13 (0.90–1.43)	0.304
PAT	292.0 ± 121.8	311.5 ± 149.8	0.83 (0.62–1.11)	0.217
GLO	326.1 ± 86.82	311.2 ± 81.86	1.18 (0.93–1.49)	0.168
Variance				
LF	228.2 ± 62.5	209.4 ± 50.8	1.41 (1.14–1.75)	*0.002*
LT	159.4 ± 63.0	151.1 ± 43.8	1.19 (0.93–1.54)	0.160
MF	328.2 ± 82.3	316.3 ± 82.4	1.14 (0.91–1.44)	0.260
MT	232.1 ± 74.7	224.1 ± 66.0	1.10 (0.86–1.39)	0.455
PAT	205.2 ± 83.0	233.9 ± 91.1	0.65 (0.47–0.90)	*0.009*
GLO	230.6 ± 52.5	227.0 ± 51.1	1.06 (0.84–1.33)	0.625

Unadjusted mean T2 texture measurements ± SD are given in milliseconds

Statistical significance is assumed at a level of $p < 0.05$

Significant *p* values are printed in italics

LF lateral femoral, *LT* lateral tibial, *MF* medial femoral, *MT* medial tibial, *PAT* patellar, *GLO* global knee (all compartments combined)

from baseline PASE scores—not adjusted for other potentially confounding predictors of TKA, such as the extent of baseline cartilage damage (as assessed via modified WORMS), or the extent of meniscal extrusion or synovial activation that may have diluted to some degree our T2 findings. However we did not assess the extent of meniscal extrusion or synovial activation in our radiology readings and therefore could not include them in our statistical model. In addition, T2 relaxation time measures are considered per se biomarkers of cartilage collagen network integrity and thus cartilage damage [13]. Adjusting our T2 findings for cartilage damage (as assessed via modified WORMS) would have run counter to the initial definition and the intrinsic purpose of T2 relaxation time measurements. Moreover, the patient's decision to undergo TKA is a multifactorial process that is based not only on structural damage or cartilage quality, but also on other factors such as age, BMI, comorbidities, patient willingness, and personal beliefs, or their socioeconomic status [49–51].

Conclusion

In summary, this study assesses to our knowledge for the first time if baseline MR-based standard T2 measurements and T2 texture measurements can be utilized as radiological imaging predictors of incident TKA. Our results show that standard T2 measurements and T2 texture measurements of the LF and certain radiologically knee pathologies, such as joint effusion and bone marrow edema pattern, can serve as predictors of incident TKA 4–7 years later. However, large validation studies with longer follow-up times of more than 7 years and limited to early osteoarthritic cases are needed to elucidate the full potential of standard T2 or texture T2 parameters as possible predictors of TKA.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval The OAI multicenter study is HIPAA-compliant and received approval by the institutional review boards at each clinical site. All study participants consented in writing to the study before study participation.

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