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Defining and predicting radiographic knee osteoarthritis progression: a systematic review of findings from the osteoarthritis initiative

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Abstract

Purpose The purposes of this systematic review were to (1) identify the commonly used definitions of radiographic KOA progression, (2) summarize the important associative risk factors for disease progression based on findings from the OAI study and (3) summarize findings from radiographic KOA progression prediction modeling studies regarding the characterization of progression and outcomes.

Methods A systematic review was performed by conducting a literature search of definitions, risk factors and predictive models for radiographic KOA progression that utilized data from the OAI database. Radiographic progression was further characterized into "accelerated KOA" and "typical progression," as defined by included studies.

Results Of 314 studies identified, 41 studies were included in the present review. Twenty-eight (28) studies analyzed risk factors associated with KOA progression, and 13 studies created or validated prediction models or risk calculators for progression. Kellgren–Lawrence (KL) grade based on radiographs was most commonly used to characterize KOA progression (50%), followed by joint space width (JSW) narrowing (32%) generally over 48 months. Risk factors with the highest odds ratios (OR) for progression included periarticular bone mineral density (OR 10.40), any knee injury within 1 year (OR 9.22) and baseline bone mineral lesions (OR 7.92). Nine prediction modeling studies utilized both clinical and structural risk factors to inform their models, and combined models outperformed purely clinical or structural models.

Conclusion The cumulative evidence suggests that combinations of structural and clinical risk factors may be able to predict radiographic KOA progression, particularly in patients with accelerated progression. Clinically relevant and feasible prediction models and risk calculators may provide valuable decision-making support when caring for patients at risk of KOA progression, although standardization in modeling and variable identification does not yet exist.

Keywords Knee · Osteoarthritis · Radiographic progression · Osteoarthritis initiative · Prediction · Model

Introduction

Knee osteoarthritis (KOA) management is made challenging by the heterogeneity of the disease process and etiology, from the speed of progression to the categorization of disease severity [3]. The increasing incidence of KOA and difficulty in preventing progression presents significant societal and cost burdens for patients and the health system [44].

The focus of this study is to characterize the radiographic progression of KOA. Radiography is a simple and cost-effective method to monitor KOA progression [19]. Previous research has focused on structural progression, utilizing metrics such as joint space width (JSW) narrowing, osteophyte formation and Kellgren–Lawrence (KL) grade [18, 19]. The KL classification is described using anteroposterior (AP) knee radiographs, with a grading classification system

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based on joint space and bony changes from Grade 0 (no joint space narrowing or reactive changes) to Grade 4 (large osteophytes with marked joint space narrowing, sclerosis and bony deformity) [27]. However, there is no consensus on which metric is best for clinical and research use, particularly for assessing and predicting radiographic disease progression.

The ability to accurately characterize and predict KOA progression may not only inform treatment decisions, but also may improve the design and efficacy of clinical studies by better targeting sample populations. The osteoarthritis initiative (OAI) continues to be a multi-center, longitudinal, prospective observational cohort study with a public database to support the investigation of the natural history of, and risk factors for, KOA onset and progression over 96 months. This makes the OAI database the ideal source for evaluating and predicting KOA progression over a longitudinal timeframe. The most recent review of prognostic factors for radiographic KOA progression was in 2015 [2]. Since then, there have been advances in imaging technology captured by the OAI database and studies utilizing newer methodologies such as deep learning that provide a more updated evidence base for better understanding radiographic KOA progression. Consequently, published studies that have utilized this dataset to investigate KOA progression are the focus of this systematic review. The goals of this review were to (1) identify the commonly used definitions of radiographic KOA progression, (2) summarize the important associative risk factors for disease progression based on findings from the OAI study and (3) summarize findings from radiographic KOA progression prediction modeling studies regarding the characterization of progression and outcomes.

Materials and methods

The OAI is a multi-center, longitudinal observational study on the risk factors for KOA onset and progression sponsored by the National Institutes of Health [37]. Comprehensive imaging, biochemical, clinical and genetic measurements from 4796 men and women ages 45–79 years with or at risk for KOA were collected over 8 years of clinical follow-up [37]. Screening and baseline data collection occurred between February 2004 and May 2006, and patient follow-up in the clinic was recorded up to 96 months after enrollment.

Study design

A systematic electronic literature search was performed in July 2021 to identify articles that studied radiographic KOA progression using the OAI database. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were implemented [30]. PubMed and Embase databases (January 2003–July 2021) were searched for articles including nested-cohort and case–control studies of risk factors, and prediction models for radiographic KOA progression that utilized data from the OAI database, using various combinations of the following key phrases: (osteoarthritis initiative), (knee), (radiograph*), (progress*), (predict*) and (model*). Studies that did not define radiographic progression or had the sole outcome measures of knee replacement, incident radiographic KOA, or symptomatic OA with no mention of radiographic progression were excluded.

Eligible studies fell into two categories: "Associated risk studies," or studies that did not involve predictive modeling of progression and generally analyzed few specific independent variables as possible correlative risk factors for KOA progression, and "Predictive modeling studies," or studies that sought to model and predict radiographic KOA progression using various methods and risk factor variables. Two main categories of risk factors of radiographic KOA progression were identified from a preliminary review of these studies: (a) structural factors and (b) clinical factors. Structural factors included imaging-based measurements and signs that can be determined using radiography, magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DXA). Clinical factors included any variable collected in the "AllClinical" files from the OAI database that included subjective symptom questionnaires and functional measurements, as well as comorbidity and other patient-level data [37]. A predefined data extraction protocol was used to systematically extract data from studies (Appendix 1). Each study's definition of and metrics used to classify radiographic progression were examined. Radiographic progression was further characterized into "accelerated osteoarthritis" (AKOA) or "typical progression" as defined by respective studies as either accelerated (KL0/1 to KL3/4 up to 48 months) or typical (any other increase in KL) to account for the heterogeneity of disease progression (Appendix 2).

The quality of the included studies and risk of bias were assessed. For nested case–control and cohort studies, the Newcastle–Ottawa Scale (NOS) assessments were utilized. For predictive modeling studies, the Prediction model Risk of Bias Assessment Tool (PROBAST) was used to assess risk of bias and applicability of models.

Statistical analysis

The extracted data were pooled, and the frequencies of the various KOA progression definitions and risk factors identified were reported for the associated risk and predictive modeling studies separately. Odds ratios (OR), hazard ratios (HR) and the respective 95% confidence intervals (CI) for

associated risk studies were reported when available. OR/HR subcategorizations of 0–1, 1–2 and > 2 were utilized to report and compare the pooled results between studies. The mean and ranges for the predictive performance of the models were analyzed and reported when the area under the curve (AUC), sensitivity and specificity data were available. The general convention of AUC interpretation was utilized, with AUC between 0.7 and 0.8 determined as having fair discrimination or predictive power, and AUC > 0.8 determined as having strong discrimination or predictive power. When studies reported p values, the threshold for statistical significance was set uniformly to $p < 0.05$. All descriptive statistics were analyzed using IBM SPSS Statistics (IBM Corp. Version 27.0. Armonk, NY. 2020).

Results

There were 314 studies based on the OAI database that were identified using the search protocol (Fig. 1). Of these studies, 41 articles met inclusion criteria with clear definitions of radiographic KOA progression described. There were 28 studies that analyzed various risk factors for progression, with specific definitions of radiographic KOA progression as the outcome variables (Table 1) [4, 5, 8, 9, 12–17, 21, 25, 26, 28, 31, 32, 34, 35, 38, 39, 41, 43, 46–51]. The 13 other studies out of the 41 total created or validated prediction models, tools, or risk calculators for radiographic KOA progression (Table 2) [1, 7, 10, 11, 18, 20, 22–24, 29, 33, 36, 40]. The quality assessments of associated risk and predictive modeling studies are summarized in Tables 3 and 4, respectively.

Definition of radiographic progression

The KL grade was most commonly used to characterize radiographic KOA progression. The breakdowns of definitions and characterizations of KOA progression for associated risk studies are summarized in Table 5 and for predictive modeling studies in Table 6.

The studies that did not subclassify based on accelerated versus typical OA progression primarily characterized progression as any increase in KL grade or JSW narrowing

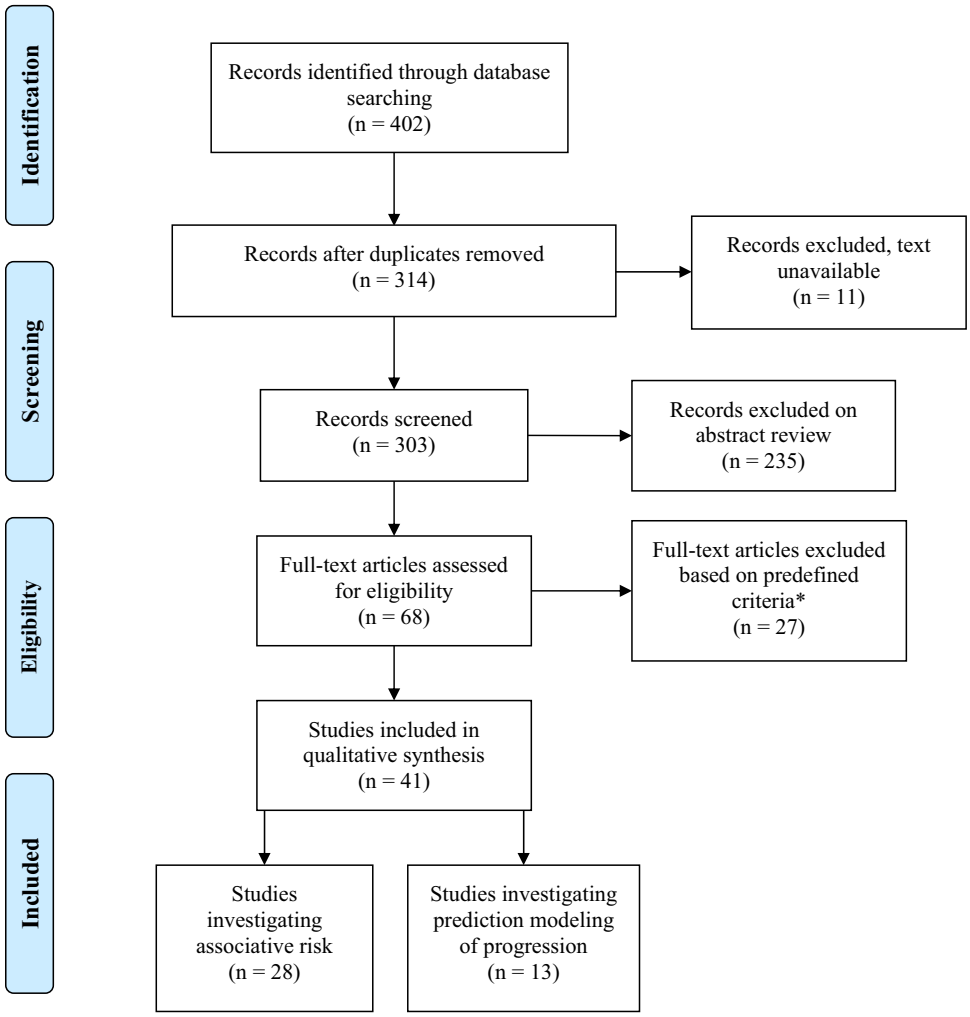

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of included studies [41]. (Asterisk) Studies that did not define radiographic progression or had the sole outcomes measure of knee replacement, incident radiographic knee osteoarthritis, or symptomatic osteoarthritis with no mention of radiographic progression were excluded. From: Moher et al. [52]

Table 1 Studies investigating associative risk factors for knee osteoarthritis progression [4, 5, 8, 9, 12–17, 21, 25, 26, 28, 31, 32, 34, 35, 38, 39, 41, 43, 46–51]

Author	Year	Journal	*n*	Definition of accelerated progression (AKOA)	Definition of typical progression	Risk factors	AKOA primary odds ratios (95% CI)	Typical KOA primary odds ratios (95% CI)
Davis et al.	2019	*BMC Musculoskelet Disord*	375	KL0/1 to KL3/4 by 48 months	Increase in KL grade 1 + over 48 months (not accelerated)	Degenerative cruciate ligaments	**2.13 (1.19, 3.82)**	**2.16 (1.23, 3.79)**
Driban et al.	2014	*Arthritis Care Res*	1930	KL0/1 to KL3/4 by 48 months	Increase in KL grade 1 + over 48 months (not accelerated)	Knee injury	**3.37 (1.82, 6.25)**	0.99 (0.61, 1.61)
Driban et al.	2016	*Clin Rheumatol*	241	KL0/1 to KL3/4 by 48 months	Increase in KL grade 1 + over 48 months (not accelerated)	Primary: WOMAC pain Secondary: disability, global impact of arthritis, chair to stand, pace	AKOA vs Typical KOA Pain **2.00 (1.33, 3.00)** Disability **1.68 (1.10, 2.55)** Global arthritis **1.89 (1.18, 3.03)**	–
Driban et al.	2016	*BMC Musculoskelet Disord*	327	KL0/1 to KL3/4 by 48 months	Increase in KL grade 1 + over 48 months (not accelerated)	Coronal tibial slope and femorotibial angle	**1.15 (1.01, 1.32)**	1.04 (0.91, 1.19)
Edd et al.	2021	*J Clin Med*	19	KL1 to KL2 to KL3 in 5 years	–	Femoral cartilage T2 changes and thickness	–	–
Everhart et al.	2019	*J Orthop Res*	1317	–	Increase in KL grade 1 + (mean f/up 59 months)	Tibiofemoral full-thickness defects (bipolar "kissing" medial compartment lesion)	–	**HR 3.05 (1.85, 4.86)**
Felson et al.	2013	*Ann Rheum Dis*	1562	–	Increase in KL grade 1 + ; mJSN worsening over 12 months	Incident disease	–	**4.00 (2.40, 6.70)**
Foreman et al.	2019	*Skeletal Radiol*	149	KL0/1 to KL3/4 by 24 months and 48 months	–	Meniscal lesions (WORMS), meniscal extrusion, and root tears	**2.82 (1.33, 6.00)**	–
Foreman et al.	2020	*Cartilage*	274	KL0/1 to KL3/4 by 48 months	KL0/1 to KL2 in 48 months	Meniscal extrusion, meniscal root tears, medial tibia cartilage lesion	Root tear **4.64 (1.61, 13.34)** Extrusion **6.30 (2.57, 15.49)**	–
Fuerst et al.	2021	*Arthritis Care Res*	201	–	mJSW decrease ≥ 0.7 mm in 24–48 months	Superficial medial cartilage relaxation time	–	–
Harkey et al.	2019	*Clin Anat*	129	KL0/1 to KL3/4 by 12 months	Increase in KL grade 1 + over 48 months (not accelerated)	Tibiofemoral cartilage change	AKOA vs Typical KOA 2.20 (0.90, 5.14)	–

Table 1 (continued)

Author	Year	Journal	*n*	Definition of accelerated progression (AKOA)	Definition of typical progression	Risk factors	AKOA primary odds ratios (95% CI)	Typical KOA primary odds ratios (95% CI)
Kawahara et al.	2019	*BMC Musculoskelet Disord*	3728	–	Over 24 months OA Change: KL0/1 to KL2/3 Mild Change: KL2 to KL3 Severe Change: KL2/3 to KL4	Stage-specific meniscal features (longitudinal diameter and wedge thickness, width, and angle)	–	Larger longitudinal diameter and meniscal width, and smaller meniscal angle predicts progression ($r = 0.4$–0.56)
Kemnitz et al.	2017	*Osteoarthritis Cartilage*	1785	–	mJSW decrease ≥ 0.7 mm in 24 months	Thigh muscle strength	–	No association with radiographic progression ($p > 0.05$)
Kwee et al.	2018	*Radiology*	600	–	mJSW decrease > 0.7 mm after 48 months	Mucoid degeneration of ACL in patients with less baseline cartilage surface area damage	–	**2.07–2.48 (1.10–5.58)**
Lo et al.	2018	*Clin Rheumatol*	1203	–	Increase in KL grade 1 + ; mJSN worsening over 48 months	Self-selected running	–	0.90 (0.60, 1.30)
Lo et al.	2018	*Semin Arthritis Rheum*	444	–	mJSN worsening over 12 months	Medial:lateral periarticular bone mineral density	–	Highest baseline quartile vs lowest quartile (unadjusted) **10.40 (3.50, 30.60)**
Lu et al.	2017	*Arthritis Care Res*	2092	–	Increase in KL grade 1 + over 48 months	Dietary fat intake (Block Brief Food Frequency Questionnaire)	–	SFA highest quartile **HR 1.60 (1.02, 2.51)** PUFA highest quartile **HR 0.70 (0.53, 0.93)**
MacKay et al.	2018	*Eur Radiol*	244	–	mJSW decrease ≥ 0.7 mm over 36 months	Composite subchondral bone texture score	–	Initial **2.13 (1.41, 3.40)** 12–18 month change **3.76 (2.04, 7.82)**
Palmer et al.	2020	*KSSTA*	955	–	JSN narrowing > 0.7 mm over 24 months	Medial proximal tibial angle	–	–
Rathbun et al.	2017	*Clin Rheumatol*	2185	–	Osteophyte grade and JSN grade worsening over 48 months	Depressive symptoms (CES-D)	–	1 year 0.40 (0.14, 1.15) 3–4 years 1.89 (0.71, 5.06)
Roemer et al.	2018	*Arthritis Care Res*	181	–	KL0-2 to KL3/4 prior to KR over 60 months	BMLs, Hoffa synovitis, effusion synovitis, WOMAC pain and ADL, KOOS pain and QOL	–	Baseline BMLs **7.92 (3.45, 18.16)**

Table 1 (continued)

Author	Year	Journal	*n*	Definition of accelerated progression (AKOA)	Definition of typical progression	Risk factors	AKOA primary odds ratios (95% CI)	Typical KOA primary odds ratios (95% CI)
Sharma et al.	2017	*Arthritis Rheumatol*	4796	–	mJSN worsening by whole grade and by partial grade up to 12 months	Varus thrust	–	Whole grade **1.49 (1.21, 1.85)** Partial grade **1.68 (1.39, 2.02)**
Waarsing et al.	2015	*Rheumatology*	518	–	Increase in KL grade 1 + or mJSN worsening over 24 months	Radiographic scores per compartment, MRI measures of cartilage and denuded bone and clinical factors	–	–
Wang et al.	2018	*Arthritis Res Ther*	4369	–	Incident: KL0/1 to KL ≥ 2 over 48 months Progression: KL2/3 to 1 + increase over 48 months	WOMAC pain	–	Baseline pain **1.07 (1.03, 1.10)** Persistent pain **1.82 (1.28, 2.60)**
Wang et al.	2019	*Rheumatology*	4115	–	Increase in KL grade 1 + over 48 months	Knee effusion volume	–	**1.28 (1.20, 1.37)**
Wirth et al.	2017	*Osteoarthritis Cartilage*	777	–	mJSW decrease ≥ 0.7 mm over 48 months	Cartilage thickness change	–	**3.40 (2.60, 4.30)**
Xu et al.	2020	*Am J Clin Nutr*	2757	–	Increase in KL grade 1 + and JSW worsening up to 72 months	Block Brief Food Frequency Questionnaire	–	Western foods **HR 1.30 (1.05, 1.61)** Prudent foods **HR 0.79 (0.64, 0.98)**
Zeng et al.	2019	*Osteoarthritis Cartilage*	684	–	Increase in KL grade 1 + or KR over 48 months and mJSW worsening ≥ 0.7 mm	Intra-articular Corticosteroid (IAC) injection	–	IAC Initiation **HR 3.02 (2.19, 4.16)** IAC continuation **HR 4.67 (2.92, 7.47)**

Boldface indicates statistically significant odds ratio at $p < 0.05$

Table 2 Studies investigating prediction modeling for knee osteoarthritis progression [1, 7, 10, 11, 18, 20, 22–24, 29, 33, 36, 40]

Author	Year	Journal	*n*	Inclusion	Prediction modeling	Covariates	Results	Definition of accelerated progression (AKOA)	Definition of typical progression
Attur et al.	2020	*Arthritis Res Ther*	204	KL2/3	Support vector machines for predictive multivariate models	PBL gene expression, WOMAC pain, VAS pain, JSW, osteophytes, MRI BML scores, age, sex, BMI	AUC 0.75 OR 19.10	mJSW narrowing of ≥ 0.5 mm at 24 months	-
Driban et al.	2018	*J Orthop Res*	162	KL0/1	Classification and Regression Tree risk classification	Serum CRP, GSP, glucose, age, gender, BMI, coronal tibial slope and femorotibial alignment	Sens 44% Spec 94% PPV 77% NPV 77%	KL0/1 to KL3/4 by 48 months	Increase in KL grade 1 + over 48 months (not accelerated)
Dunn et al.	2019	*Sci Rep*	116	KL2/3	PBMC epigenetic machine learning discriminant model	Age, gender, BMI, ethnicity, smoking, NSAID use, WOMAC, blood differential, T2DM, MI, stroke, lung disease, cancer	AUC 0.81 OR 11 Sens 74% Spec 70%	N/A	mJSW decrease ≥ 0.7 mm over first 24 months and sustained at 48 months
Dunn et al.	2020	*Osteoarthritis Cartilage*	2701	Incidence and Progression cohorts	Interval-censored Cox proportional hazards model for time to eskOA	Risk stratification using all variables from baseline OAI AllClinical dataset and imaging measurements	AUC 0.87 Sens 80% Spec 75%	N/A	Increase to KL4 and WOMAC pain + disability ≥ 12 by 48 months
Guan et al.	2020	*Osteoarthritis Cartilage*	1950	KL0-3	Deep learning risk assessment model using radiography	Age, gender, race, BMI, injury history, KL, tibiofemoral angle	Traditional AUC 0.66 Deep learning AUC 0.80 Combined AUC 0.88 Sens 80.5% Spec 80.5%	N/A	mJSW decrease ≥ 0.7 mm over 48 months
Halilaj et al.	2018	*Osteoarthritis Cartilage*	1243	Incidence cohort	Mixed-effects mixture model	JSW, WOMAC pain and other baseline measures selected using least absolute shrinkage and selection regression (LASSO)	AUC 0.86	N/A	Progression categorized by mixed-effects model based on JSN

Table 2 (continued)

Author	Year	Journal	*n*	Inclusion	Prediction modeling	Covariates	Results	Definition of accelerated progression (AKOA)	Definition of typical progression
Harkey et al.	2020	*BMC Musculoskelet Disord*	375	KL0/1	MRI-based composite quantitative knee scores	Cartilage damage, BML volume, effusion synovitis, BMI, age, race, activity, pain	OR > 2 AKOA vs no KOA	KL0/1 to KL3/4 by 48 months	Increase in KL grade 1 + over 48 months (not accelerated)
Janvier et al.	2017	*Osteoarthritis Cartilage*	1124	KL2/3	Subchondral tibial bone texture analysis using fractal dimensions on radiographs	Age, BMI, gender, mJSN	FD AUC 0.71 JSN AUC 0.71 Mixed AUC 0.77	N/A	JSN worsening over 48 months
Joseph et al.	2018	*J Magn Reson Imaging*	641	KL0-2	Statistical prediction modeling using logistic regression	Age, gender, BMI, KL, knee alignment, injury, cartilage defects, meniscus tears	Model 1 AUC 0.67 Model 2 AUC 0.71 Model 3 AUC 0.72	N/A	KL increase to 3 or 4 or KR over 8 years
LaValley et al.	2017	*Arthritis Res Ther*	533	Progression cohort	BMD enhanced prediction model using logistic regression	Age, gender, BMI, knee pain, injury, hand OA, BMD	Base model AUC 0.65 Combined model AUC 0.73	N/A	JSN worsening over 48 months
Lo et al.	2019	*Clin Rheumatol*	4480	KL0-4	Ambulation Adjusted Score (AASK) using WOMAC and average hours of daily walking	Age, gender, BMI, KL, pain, walking	AASK outperformed WOMAC ($p < 0.05$)	N/A	Increase in KL 1 + over 48 months
Mononen et al.	2019	*Ann Biomed Eng*	21	KL0	Atlas-based prediction modeling using MRI	Age, BMI, KL, meniscus	AUC 0.87	N/A	Increase in KL over 48 months
Riddle et al.	2016	*Osteoarthritis Cartilage*	4112	KL0/1	Multivariable logistic regression prediction model	Age, gender, OA in other joints, BMI, depression, WOMAC, injury, frequency of symptoms, prior surgery, alignment	AUC 0.77	KL0/1 to KL3/4 by 48 months	N/A

Table 3 Newcastle–Ottawa Scale for cohort and case–control studies

Author	Year	Selection	Comparability	Exposure/ Outcome
		(★★★★)	(★★)	(★★★)
Davis et al.	2019	★★★	★★	★★★
Driban et al.	2014	★★★	★★	★★
Driban et al.	2016	★★★	★★	★★
Driban et al.	2016	★★★	★★	★★
Edd et al.	2021	★★	★★	★★★
Everhart et al.	2019	★★★	★★	★★
Felson et al.	2013	★★★	★★	★★
Foreman et al.	2019	★★★	★★	★★
Foreman et al.	2020	★★★	★★	★★★
Fuerst et al.	2021	★★★	★★	★★★
Harkey et al.	2019	★★★	★★	★★
Kawahara et al.	2019	★★★	★★	★★
Kemnitz et al.	2017	★★★	★★	★
Kwee et al.	2018	★★★	★★	★★
Lo et al.	2018	★★★	★★	★★★
Lo et al.	2018	★★	★★	★★
Lu et al.	2017	★★★	★★	★★★
MacKay et al.	2018	★★★	★★	★★★
Palmer et al.	2020	★★★	★★	★★
Rathbun et al.	2017	★★★	★★	★★★
Roemer et al.	2018	★	★★	★★★
Sharma et al.	2017	★★	★★	★★★
Waarsing et al.	2015	★★★	★★	★★★
Wang et al.	2018	★★★	★★	★★
Wang et al.	2019	★★★★	★★	★★
Wirth et al.	2017	★★★	★★	★★★
Xu et al.	2020	★★★	★★	★★★
Zeng et al.	2019	★★★	★★	★★★

greater than 0.7 mm up to 72 months (15%), 48 months (50%), 24 months (20%) and 12 months (15%). Of note, Kawahara et al. categorized the severity of progression with "OA Change" as KL0 and KL1 increasing to KL2 or KL3, "Mild Change" as KL2 increasing to KL3 and "Severe Change" as KL2 and KL3 increasing to KL4 over 24 months [25].

Nine studies defined AKOA progression as an increase to KL3 or KL4 within 48 months [4, 5, 7–9, 15, 16, 22, 40]. Foreman et al. further sub-characterized AKOA to 24-month and 48-month groups [16], while Harkey et al. defined AKOA as an increase to KL3 or KL4 from KL0 and KL1 within 12 months [21]. Attur et al. uniquely defined AKOA as JSW narrowing of greater than 0.5 mm within 24 months [1].

Risk factors and outcomes-associated risk studies

Among the associated risk studies for progression, there were 18 studies (64%) that examined structural risk factors. Fourteen studies analyzed MRI measures, including baseline and yearly changes in cartilage volume, meniscal and ligament changes, meniscal extrusion, meniscal root tears and knee effusion volume. One study utilized DXA scans to analyze how static alignment of the knee affects periarticular bone using the proximal tibial plateau periarticular bone mineral density (paBMD) measures, while four studies utilized radiography to analyze coronal tibial slope, femorotibial alignment and angle and JSW narrowing (Table 5) [9, 14, 32, 38, 43]. Pain was the most common clinical risk factor evaluated by these studies.

Notably, among associated risk studies on AKOA, any knee injury within the observational period (OR 3.37, 95% CI 1.82–6.25) and within 1 year of accelerated progression (OR 9.22, 95% CI 4.5–18.90) showed the greatest odds ratios for AKOA progression compared to no KOA progression (Table 1) [5]. Degenerative cruciate ligaments,

Table 4 Prediction model study risk of bias assessment tool (PROBAST) assessment

Author	Year	Bias risk	Applicability Concern	Concern
Attur et al.	2020	High	Low	Small sample
Driban et al.	2018	High	Unclear	Small sample, no external validation
Dunn et al.	2019	High	Unclear	Small sample, no external validation
Dunn et al.	2020	Low	Unclear	No external validation
Guan et al.	2020	Low	Unclear	No external validation
Halilaj et al.	2018	Unclear	Unclear	No external validation, no censoring/competing risk
Harkey et al.	2020	High	High	Small sample, no validation
Janvier et al.	2017	Low	High	No validation
Joseph et al.	2018	Unclear	Unclear	Only right knees, no external validation
LaValley et al.	2017	High	Unclear	Small sample, no external validation
Lo et al.	2019	Unclear	High	No censoring/competing risk, no validation
Mononen et al.	2019	High	High	Extremely small sample
Riddle et al.	2016	High	Unclear	Different outcome criteria between test and validation

Table 5 Primary risk factors and outcomes observed for associative risk studies

	Study RKOA progression classifications		
	Any progression $n=20$	Accelerated progression $n=8$	Total $n=28$
Outcome variable			
KL	6 (30%)	7 (87%)	13 (46%)
JSW	9 (45%)	1 (13%)	10 (36%)
Both	5 (25%)	–	5 (18%)
Study inclusion			
No RKOA (KL 0/1)	1 (5%)	8 (100%)	9 (32%)
RKOA (KL 2/3)	3 (15%)	–	3 (11%)
Up to KL = 3	9 (45%)	–	9 (32%)
All KL grades	7 (35%)	–	7 (25%)
Progression definition			
KL + 1/JSN, 12 mos	3 (15%)	–	3 (11%)
KL + 1/JSN, 24 mos	4 (20%)	–	4 (14%)
KL + 1/JSN, 48 mos	10 (50%)	–	9 (32%)
KL + 1/JSN, 72 mos	3 (15%)	–	3 (11%)
KL0/1 to KL ≥ 3, 12 mos	–	1 (13%)	1 (4%)
KL0/1 to KL ≥ 3, ≥ 48 mos	–	7 (87%)	7 (25%)
Primary structural variables			
MRI metrics	9 (45%)	5 (63%)	14 (50%)
DXA metrics	1 (5%)	–	1 (4%)
Other X-ray metrics	3 (15%)	1 (13%)	4 (14%)
Not applicable	7 (35%)	2 (25%)	9 (32%)
Primary clinical variables			
Pain	4 (20%)	1 (13%)	5 (18%)
Injury	–	2 (25%)	2 (7%)
Clinical function	2 (10%)	–	2 (7%)
Depression	1 (5%)	–	1 (4%)
Lifestyle factors	2 (10%)	–	2 (7%)
Medications	1 (5%)	–	1 (4%)
Not applicable	9 (45%)	5 (63%)	14 (50%)

Table 6 Primary risk factors and outcomes observed for prediction modeling studies

	Study RKOA progression classifications		
	Any progression $n=9$	Accelerated progression $n=4$	Total $n=13$
Outcome variable			
KL	4 (44%)	3 (75%)	7 (54%)
JSW	5 (56%)	1 (25%)	6 (46%)
Study inclusion			
No RKOA (KL 0/1)	2 (22%)	3 (75%)	5 (38%)
RKOA (KL 2/3)	2 (22%)	1 (25%)	3 (23%)
Up to KL = 3	2 (22%)	–	2 (15%)
All KL grades	3 (33%)	–	3 (23%)
Progression definition			
JSN ≥ 0.5 mm, 24 mos	–	1 (25%)	1 (8%)
KL + 1/JSN, 48 mos	6 (67%)	–	6 (46%)
KL ≥ 3, 48 mos	1 (11%)	3 (75%)	4 (31%)
KL ≥ 3, 8 yrs	1 (11%)	–	1 (8%)
Other JSN, 8 yrs	1 (11%)	–	1 (8%)
Risk factors utilized			
Structural	2 (22%)	1 (25%)	3 (23%)
Clinical	1 (11%)	–	1 (8%)
Both	6 (67%)	3 (75%)	9 (69%)
Model results			Mean (range)
AUC ($n=10$)	–	–	0.81 (0.71–0.88)
Sensitivity ($n=4$)	–	–	70% (44–80.5)
Specificity ($n=4$)	–	–	80% (70–94)

meniscal extrusion and meniscal root tears were found to be significantly associated with AKOA progression with OR > 2, and pain, disability scores, coronal tibial slope and femorotibial angle were moderately associated with AKOA with OR between 1 and 2 [4, 8, 9, 15, 16].

For studies that investigated any radiographic KOA progression, measures of periarticular bone mineral density (OR 10.40, 95% CI 3.50–30.60) and bone marrow lesions (OR 7.92, 95% CI 3.45–18.16) showed the greatest odds for progression, followed by intra-articular corticosteroid injections (HR 4.67, 95% CI 2.92–7.47) [32, 41, 51]. The data for intra-articular corticosteroid injections suggested that the treatment, particularly with continued use, was associated with worsening KOA irrespective of pain.

Risk factors and outcomes: predictive modeling studies

The prediction modeling studies incorporated numerous risk factors to provide the models with enough training variables or to ensure the optimal mix of risk factors within the OAI dataset (Table 6). Nine of the modeling studies (69%) utilized mixtures of both structural and clinical risk factors to maximize the predictive potential of KOA progression over time. This was evidenced by five of these studies comparing the performance of the models using only structural, only clinical, and combined risk factors, and concluding that the combined models outperformed the separate models

($p < 0.05$) [1, 18, 23, 24, 29]. One study developed an Ambulation Adjusted Score based on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores and average hours of daily walking as a clinical tool for monitoring KOA progression, while another constructed a risk score based on the top nine risk variables predicting progression to end-stage KOA identified from all variables in the OAI database—these included the KL Grade, Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life score, OARSI medial joint space narrowing, flexion contracture/hyperextension, knee pain severity in the past 30 days, the WOMAC disability and pain scores, and baseline symptomatic KOA status calculated by the OAI investigators as any baseline symptom in the affected knee, such as pain and stiffness [11, 33]. Of note, Dunn et al. utilized a biomarker, peripheral blood mononuclear cells (PBMC), and analyzed the epigenetic patterns and methylation to create a prediction tool for radiographic KOA progression [10].

Among the 13 prediction modeling studies, the overall mean sensitivity of the models was 70% (range 44–80.5), mean specificity was 80% (range 70–94) and the mean AUC was 0.81 (0.71–0.88) (Table 6).

Discussion

The most important finding of this study was that KL grading was most commonly utilized to define radiographic KOA progression. However, this review demonstrated that there remains wide variability and no consensus on what definition of radiographic KOA progression is best for use in research and clinical practice.

In this review, half of the studies utilized the KL classification to define radiographic KOA progression, roughly one-third utilized JSW narrowing and the rest a combination of both KL and JSW narrowing. In addition, the timeframe of progression was also found to be variable between studies. While most studies defined progression within 48 months, timeframes up to 8 years were also utilized. This variability in classification and timeframe demonstrates the need for standardization within the scientific community in defining KOA progression. This review found KL grading and a timeframe of 48 months to be most commonly used, similar to findings by Bastick et al. in a separate meta-analysis of KOA progression [2].

Of note, as the heterogeneity of the phenotype of KOA is further elucidated, interest in AKOA has added another layer of complexity to classifying radiographic progression. The present review found most studies to define AKOA progression as KL increase from 0/1 to 3/4 within 48 months, with a few utilizing timeframes between 12 and 60 months or JSW narrowing > 0.5 mm. These findings are consistent with a review on AKOA by Driban et al. that defined AKOA as rapid KL increase within 48 months [6]. They also found studies in the literature with variable descriptions of progression, from "fast" to "rapid" and "accelerated". Definitions ranged from > 0.25 to > 2 mm JSW narrowing within 1 year or KL change greater or equal to 2 within 4–5 years. The definition of AKOA utilizing KL grading and 48 months as the timeframe is offered for standardization of reports.

The findings in this review add to the evidence from meta-analyses by Culvenor et al. and Bastick et al. with updated risk factors and imaging modalities [2, 4]. Bastick et al. reported strong evidence that varus alignment and baseline pain were associated with radiographic KOA progression [2]. In their analysis, conflicting evidence was noted for baseline radiographic or clinical OA severity and past knee injury, while limited evidence was found for other imaging-based risk factors such as meniscal damage, radiographic fractal signature analysis that determines three-dimensionality based on the two-dimensional image and MRI-detected subchondral bone cysts. The more recent studies published after Bastick et al.'s meta-analysis [2] summarized in this present review suggest that there is a trend towards greater association with radiographic KOA progression utilizing imaging-based objective measurements compared to subjective scoring and tools. Further studies investigating these imaging-based risk factors will better inform the strength of the association with radiographic KOA progression.

There were five prediction modeling studies with tools that would be considered to have strong predictive power (AUC > 0.8), with the rest having fair predictive power (AUC > 0.7). These results were comparable, if not better than prediction tools developed outside of the OAI database, further supporting the utility of this database in assessing predictive modeling studies. Runhaar et al. developed a prediction model for early KOA progression using data from the Cohort Hip and Cohort Knee (CHECK) study with an AUC of between 0.746 and 0.764, while Tiulpin et al. developed a multimodal machine learning-based KOA prediction tool that yielded an AUC of 0.79 [42, 45]. Evidence suggests that generally, studies with large patient numbers, diverse yet targeted prediction variables and nonlinear models performed well.

While the OAI database is the largest longitudinal database on KOA, limitations of this review include evaluation of retrospective studies drawing from one patient population with exclusion and inclusion criteria limited to those set by the initial OAI study and having no access to individual patient charts. While internal validation of the risk associations and prediction models is adequate, it is difficult to generalize the results of these studies to the larger population without validation using more datasets drawn from different sample populations. Even so, Riddle et al. validated their clinical prediction rule for estimating the likelihood of developing incident radiographic KOA using both the OAI

and the Multicenter Osteoarthritis Study, and found that the AUC was similar in both sets at 0.81 and 0.79, respectively [40]. This shows promise for the generalizability of the OAI database, and further study should focus on the external validity of risk factors and prediction models derived from the OAI database.

Conclusions

Cumulative evidence suggests that combinations of structural and clinical risk factors may be best to predict radiographic KOA progression. To better understand what risk factors to identify, a consensus on the definition of radiographic KOA progression will aid in comparing and designing future studies. While current standardization in modeling and variable inputs do not yet exist, the collection of studies based on the OAI database shows that following KL grade over time may be a valid outcomes proxy that can be utilized to create prediction algorithms, models and tools for radiographic KOA progression.

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Declarations

Conflict of interest The authors declare they have no relevant conflicting interests.

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