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Review

Predicting Knee Osteoarthritis from Conventional Radiography: Current Radiographic Biomarkers, Artificial Intelligence, and a Stage-Specific Clinical Framework

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Abstract

This narrative review aimed to synthesize evidence on biomarkers derived from conventional knee radiographs for predicting incident and progressive knee osteoarthritis (KOA) and to propose an evidence-informed, stage-specific framework for biomarker selection. PubMed/MEDLINE was searched from inception to July 2026 using a structured strategy to identify longitudinal studies evaluating radiographic predictors of KOA. Eligible studies evaluated radiographic predictors of incident or progressive KOA and reported quantitative predictive performance. Studies lacking an eligible predictor derived from conventional knee radiographs, using non-radiographic biomarkers as principal predictors, cross-sectional or diagnostic-only designs, or outcomes unrelated to KOA incidence or progression were excluded. Thirty-eight unique studies were included: eleven addressed incidence only, 23 progression only, and four both outcomes. Kellgren–Lawrence grade, joint-space width, and joint-space narrowing remained clinically interpretable reference measures, particularly for structural progression. Bone morphology, alignment, and trabecular bone texture/fractal signature analysis provided complementary structural and biomechanical information. Radiomics and artificial intelligence enabled extraction and integration of quantitative radiographic features, with promising but heterogeneous performance. No advanced biomarker consistently outperformed conventional or longitudinal quantitative measures across independent cohorts. Conventional radiography therefore remains a scalable basis for KOA risk prediction, while clinical translation of advanced biomarkers requires methodological standardization, calibration, explainability, and prospective external validation across populations and radiographic acquisition systems before routine implementation.

Keywords: knee osteoarthritis; radiography; prediction; biomarkers; trabecular bone texture; radiomics; artificial intelligence

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Academic Editor: Jason Shearn

Received: 23 September 2026
Revised: 17 November 2026
Accepted: 19 November 2026
Published: 23 November 2026

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1. Introduction

Knee osteoarthritis (KOA) is the most common site-specific form of osteoarthritis and a major cause of chronic pain, impaired mobility, physical disability, and reduced quality of life worldwide. Its prevalence is increasing because of population growth and ageing, the rising prevalence of obesity, and greater exposure to joint injury and other biomechanical

risk factors. According to the Global Burden of Disease 2021 study, approximately 595 million people were living with osteoarthritis in 2020, with the knee representing the most frequently affected joint. The number of people with KOA is projected to increase by approximately 75% between 2020 and 2050 [1]. Beyond its effects on individuals, KOA imposes a substantial socioeconomic burden through healthcare utilization, productivity loss, informal care requirements, and the increasing demand for total knee arthroplasty.

Over the past two decades, the understanding of KOA has evolved considerably. Rather than being considered a disease confined to the articular cartilage, osteoarthritis is now recognized as a whole-joint disorder involving cartilage, subchondral bone, menisci, synovium, ligaments, periarticular muscles, and the surrounding biomechanical environment [2]. Structural deterioration results from interactions among abnormal mechanical loading, low-grade inflammation, subchondral bone remodelling, ageing, metabolic factors, previous joint injury, and individual susceptibility. Changes in several joint tissues may therefore precede the development of definite radiographic KOA, providing a potential window for early risk identification and preventive intervention.

Despite substantial advances in understanding OA pathophysiology, available therapeutic strategies remain predominantly symptomatic. Adult articular cartilage is avascular, aneural, and alymphatic and consequently has a limited intrinsic capacity to repair substantial structural damage. Although numerous disease-modifying osteoarthritis drugs (DMOADs) have been investigated, no treatment has yet achieved widespread regulatory approval and routine clinical use based on a reproducible ability to prevent or reverse structural progression [3,4]. Current management consequently relies mainly on education, exercise therapy, weight management, analgesic treatment, selected intra-articular interventions, and joint replacement for end-stage disease. These limitations emphasize the importance of identifying individuals at increased risk before extensive structural deterioration has occurred.

Prediction of both incident and progressive KOA has consequently become an important research objective. Incident-KOA prediction seeks to identify knees at risk of developing definite radiographic disease, commonly defined as progression from KL grades 0–1 to KL grade ≥ 2. Progression prediction, by contrast, concerns knees with existing radiographic or symptomatic abnormalities and estimates the risk of subsequent structural, symptomatic, or combined worsening. Accurate risk stratification could support targeted preventive strategies, enrich clinical trials with participants likely to experience measurable progression, optimize follow-up, and contribute to the development of precision approaches to KOA management.

Among available imaging modalities, weight-bearing radiography remains the principal method for structural assessment of KOA. MRI provides more detailed visualization of cartilage, menisci, synovium, ligaments, bone marrow lesions, and other joint tissues, but its higher cost, longer acquisition time, and more limited availability constrain its use for population-scale screening and repeated assessment. MRI is therefore generally reserved for specific clinical indications or research applications rather than routine longitudinal monitoring of all individuals with or at risk of KOA.

Conventional radiography is comparatively inexpensive, rapid, widely accessible, and routinely incorporated into clinical care and longitudinal cohort studies. Standardized knee radiographs have been used for structural assessment in major cohorts, including the Osteoarthritis Initiative (OAI), the Multicenter Osteoarthritis Study (MOST), and the Cohort Hip and Cohort Knee (CHECK). Their scalability makes conventional radiographs particularly suitable for epidemiological research, multicentre clinical trials, and prediction strategies intended for broad clinical implementation. Maximizing the prognostic information extracted from these routinely acquired images could therefore provide substantial clinical and research value.

Traditional radiographic assessment relies on semiquantitative measures such as the Kellgren–Lawrence (KL) and joint-space narrowing (JSN) grades, together with quantitative measurements such as joint-space width (JSW). These biomarkers remain clinically interpretable reference measures of structural severity and progression. Baseline KL and JSN grades also provide relevant information for predicting incident KOA, particularly when combined with clinical and demographic risk factors. Nevertheless, conventional visual grading may not capture subtle spatial, morphological, or textural alterations that precede definite radiographic disease or distinguish knees with similar grades but different progression trajectories.

Advances in quantitative image analysis have considerably expanded the prognostic information obtainable from conventional radiographs. Bone and joint morphology, lower-limb alignment, trabecular bone texture (TBT), fractal signature analysis (FSA), radiomics, and artificial intelligence (AI) can quantify imaging characteristics that may not be readily apparent through visual assessment. The available longitudinal evidence suggests that morphological features and TBT/FSA may provide complementary information for predicting incident KOA, whereas TBT/FSA, quantitative JSW, JSN, and AI-derived features have been more extensively evaluated for progression prediction [5–7]. However, no advanced biomarker category has consistently outperformed conventional or longitudinal quantitative measures across independent cohorts. Their incremental value depends on the population, baseline disease stage, prediction horizon, outcome definition, and validation strategy.

The expanding literature on radiographic prediction is methodologically heterogeneous. Studies differ in the radiographic biomarkers evaluated, baseline KL grades, cohort composition, follow-up duration, outcome definitions, modelling approaches, and reporting of predictive performance. Existing reviews have often organized this evidence according to imaging features or computational methods, with less emphasis on the clinical distinction between predicting disease incidence and predicting the progression of established disease. This distinction is important because the intended context of use and the most informative radiographic predictors may differ according to baseline disease status.

Accordingly, this updated narrative review aimed to critically synthesize the available evidence on biomarkers derived from conventional knee radiographs for predicting incident and progressive KOA. Particular attention was given to conventional radiographic measures, including KL grade, JSW, and JSN; bone morphology and alignment; TBT/FSA; radiomics; and AI-derived features. Differences in outcome definitions, prediction horizons, model performance, and external validation were also examined. Finally, an evidence-informed, stage-specific conceptual framework is proposed to relate radiographic biomarker selection to baseline KL grade and the intended prediction objective. This framework is intended to organize the current evidence and identify priorities for future validation rather than to serve as a validated clinical decision algorithm.

2. Methods

2.1. Study Design

A structured narrative review was undertaken to identify and critically synthesize original studies evaluating biomarkers derived from conventional knee radiographs for predicting incident or progressive knee osteoarthritis (KOA). A structured search and predefined eligibility criteria were applied, and the record-selection process was documented in a flow diagram to enhance transparency and reproducibility.

The review focused on prognostic information obtained from conventional knee radiographs. Eligible radiographic predictors included conventional semiquantitative and quantitative measures, bone geometry and morphology, lower-limb alignment, trabecular

bone texture (TBT), fractal signature analysis (FSA), radiomics, and features extracted using machine learning or deep learning methods.

This review was not designed as a systematic or scoping review; therefore, protocol registration, submission of a full PRISMA checklist, formal risk-of-bias assessment, and meta-analysis were not applicable.

2.2. Literature Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE from database inception to 2 July 2026. Several complementary searches were performed, and the resulting records were combined and de-duplicated before screening.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms relating to KOA, conventional radiography, prediction, prognosis, disease incidence and progression, and quantitative radiographic biomarkers. The core search syntax was based on combinations of the following terms:

("knee osteoarthritis"[tiab] OR "osteoarthritis of the knee"[tiab] OR "knee OA"[tiab]) AND (radiograph*[tiab] OR radiographic[tiab] OR radiological[tiab] OR "x-ray"[tiab] OR "plain radiograph*"[tiab]) AND (predict*[tiab] OR predictor*[tiab] OR prognos*[tiab] OR prognostic[tiab]) AND (progress*[tiab] OR incidenc*[tiab] OR onset[tiab] OR development[tiab] OR worsening[tiab])NOT (MRI[tiab] OR "magnetic resonance imaging"[tiab] OR ultrasound[tiab] OR ultrasonography[tiab] OR sonography[tiab] OR CT[tiab] OR "computed tomography"[tiab] OR tomography[tiab])NOT (surgery[tiab] OR surgical[tiab] OR arthroplasty[tiab] OR "total knee replacement"[tiab] OR "total knee arthroplasty"[tiab] OR arthroscopy[tiab] OR osteotomy[tiab])NOT (Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt]).

The initial search had used exclusion terms related to MRI, computed tomography, ultrasound, and surgery to improve specificity for conventional radiography studies. Because these restrictions could exclude multimodal studies that also evaluated eligible radiographic predictors, supplementary sensitivity searches were subsequently conducted without these imaging- and surgery-related exclusion blocks. Targeted searches combining the core radiographic strategy with MRI, computed tomography, ultrasound, and surgical terminology were also performed to identify potentially relevant records containing both conventional radiography and other imaging or clinical terms. The same publication-date cutoff and eligibility criteria were applied to these searches.

Studies identified through the supplementary searches were eligible when at least one predictor derived from conventional knee radiographs was explicitly evaluated for predicting an observed longitudinal KOA outcome and quantitative predictive performance was reported. The presence of MRI, computed tomography, biochemical, clinical, or other variables did not preclude inclusion when radiographic predictors were evaluated independently or as part of a multimodal prediction model.

Additional targeted searches were conducted using the names of specific biomarkers and analytical methods to identify studies that might not have been retrieved by the core search. The reference lists of relevant review articles and eligible original studies were also examined manually to identify additional potentially eligible publications. The final search results were merged, and duplicate records arising from overlapping queries were removed.

2.3. Eligibility Criteria

Studies were eligible when they fulfilled all the following criteria:

- Original human research published as a full-text article in a peer-reviewed journal;
- Prospective or retrospective longitudinal cohort study, nested case–control study, or longitudinal secondary analysis of cohort or clinical-trial data;

- Use of conventional knee radiographs as the primary source of at least one predictor, either independently or as part of a multimodal prediction model;
- Evaluation of a radiographic biomarker measured at baseline or during an initial observation interval preceding the outcome-assessment period;
- Prediction of incident KOA or subsequent structural, symptomatic, or combined KOA progression;
- Reporting of a quantitative measure of predictive performance, such as the area under the receiver operating characteristic curve, accuracy, sensitivity, specificity, predictive values, F1-score, balanced accuracy, prediction error, or another clearly defined performance measure; and
- Publication in English.

Incident KOA generally refers to the development of definite radiographic KOA in knees without definite disease at baseline, commonly progression from KL grades 0–1 to KL grade ≥ 2. Studies using another clearly defined incidence outcome, such as the combined onset of frequent knee symptoms and definite radiographic abnormalities, were also considered eligible. Studies predicting longer-term radiographic severity from knees without definite KOA at baseline were also eligible, provided that the outcome was defined using an observed longitudinal radiographic assessment.

Progressive KOA referred to worsening among knees with baseline radiographic or symptomatic abnormalities. Eligible progression outcomes included an increase in KL or OARSI JSN grade, quantitative JSW loss, development of end-stage KOA, sustained symptomatic worsening, or a predefined composite of radiographic and symptomatic progression. Total knee replacement alone was not considered an eligible progression outcome. However, studies reporting a composite outcome that included knee replacement remained eligible when the outcome also incorporated an eligible radiographic or symptomatic progression component.

Studies were excluded when they met one or more of the following conditions:

- Cross-sectional, diagnostic, or classification study without an observed longitudinal outcome;
- Risk-factor or association analysis that did not develop or evaluate a prediction model and did not report predictive-performance measures;
- Use of MRI, computed tomography, ultrasound, dual-energy X-ray absorptiometry, scintigraphy, biochemical markers, gait measurements, or other non-radiographic variables as the principal predictor, with conventional radiography used only to define the outcome;
- Absence of an eligible predictor derived from conventional knee radiographs;
- Outcome unrelated to incident or progressive KOA;
- Generation or classification of synthetic disease stages without prediction of an observed longitudinal outcome;
- Evaluation of surgical interventions or postoperative outcomes, or use of knee arthroplasty, including total knee replacement, as the principal prediction outcome;
- Review article, editorial, conference abstract, case report, animal or experimental study;
- Publication in a language other than English; or
- Insufficient information for extraction of the predictor, outcome, follow-up, or predictive results.

Multimodal studies were retained when at least one conventional radiographic biomarker contributed to the prediction model and its predictive role or incremental value could be evaluated. The concurrent use of MRI, computed tomography, biochemical biomarkers, clinical variables, or other data sources was not itself a reason for exclusion. Conversely, studies in which conventional radiographic measures served solely as outcome definitions were excluded.

2.4. Study Selection

Records retrieved from the initial and supplementary sensitivity searches were merged and de-duplicated, both within and across searches. Titles and abstracts were screened against the predefined eligibility criteria. Publications considered potentially relevant subsequently underwent full-text assessment.

Multimodal studies underwent additional full-text assessment to determine the role of conventional radiographic predictors within the model and whether quantitative predictive performance could be extracted. Studies in which radiographs were used only to define the outcome, without providing an eligible predictor, were excluded.

A principal reason for exclusion was recorded for each excluded full-text article to ensure mutually exclusive counts in the study-selection flow diagram. When several exclusion criteria applied, the reason judged to be most directly related to the review objective was recorded as the principal reason.

One reviewer (A.A.-I.) screened the titles and abstracts and assessed potentially eligible full-text articles. Cases in which eligibility was uncertain were discussed with the two other authors (E.L. and H.T.), and the final decision was reached by consensus. The final selection comprised studies addressing incidence prediction, progression prediction, or both objectives. Studies evaluating both outcomes were represented in both evidence tables but counted only once when calculating the total number of unique included studies. The complete selection process and reasons for exclusion are presented in Figure 1.

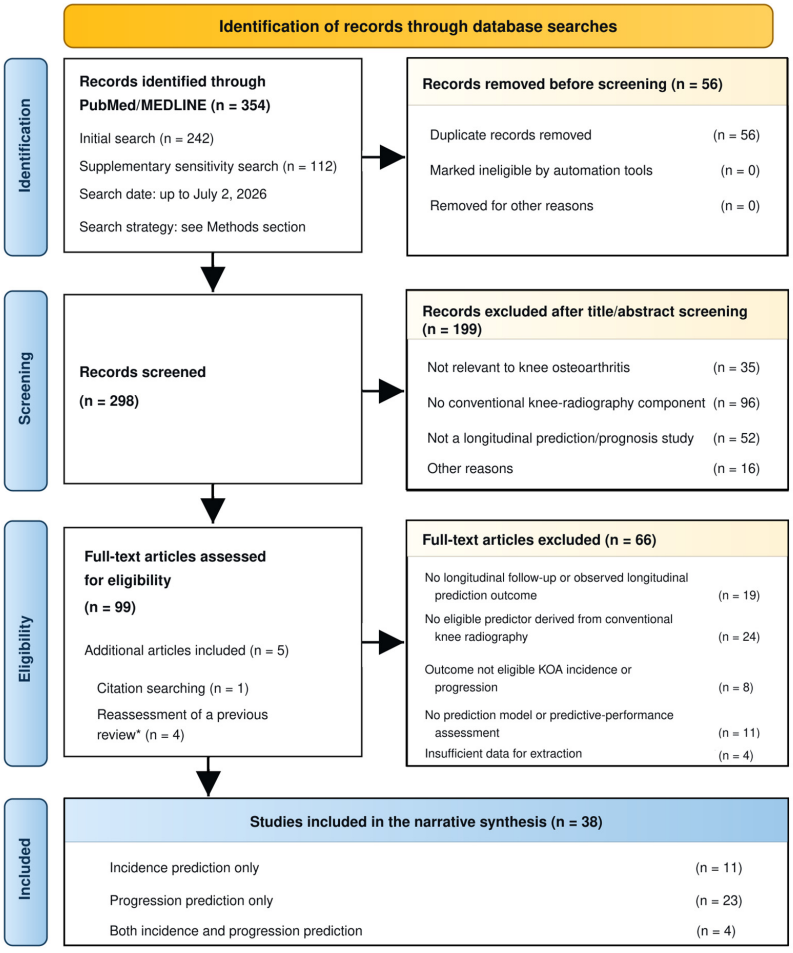

Figure 1. Flow diagram of literature identification, screening, eligibility assessment, and study inclusion. * The previous review refers to Almhdie-Imjabbar et al. (2023) [8].

2.5. Data Extraction

Data were extracted using a standardized form developed for this review. The following information was recorded when available:

- First author and publication year;
- Reference number and PubMed identifier;
- Study cohort and design;
- Sample size and unit of analysis, including participants or knees;
- Baseline radiographic disease status;
- Follow-up duration and prediction horizon;
- Radiographic acquisition or measurement approach;
- Principal radiographic biomarker or analytical method;
- Clinical prediction objective: incidence, progression, or both;
- Outcome domain: radiographic, symptomatic, or combined;
- Definition of the primary prediction outcome;
- Modelling method;
- Internal or external validation strategy;
- Principal findings; and
- Reported predictive-performance measures.

Predictive-performance measures included the area under the receiver operating characteristic curve or C-statistic, accuracy, sensitivity, specificity, positive and negative predictive values, F1-score, balanced accuracy, mean absolute error, and intraclass correlation coefficient, as applicable. For studies predicting a continuous radiographic outcome, such as future JSW, appropriate regression-performance and agreement measures were extracted. When several models were reported, priority was given to the principal model, the best-performing appropriately validated model, and comparisons demonstrating the incremental contribution of radiographic biomarkers. For multimodal studies, the composition of each relevant predictor set was recorded, including whether conventional radiographic variables were evaluated alone, added incrementally, or integrated with other data modalities. Performance estimates from multimodal models were interpreted as reflecting the complete predictor set and were not attributed exclusively to the radiographic component unless its independent or incremental contribution was specifically reported.

When model-derived quantities, such as simulated cartilage degeneration, were used as predictors, these were distinguished from directly observed longitudinal imaging outcomes. Likewise, composite outcomes incorporating radiographic, symptomatic, functional, or surgical components were recorded according to their complete original definition.

Studies predicting incident KOA are summarized in Table 1, whereas studies predicting KOA progression are presented in Table 2. Studies evaluating both objectives appear in both tables but were counted only once in the total evidence base.

Table 1. Characteristics of studies predicting knee osteoarthritis incidence.

Study (Authors, Publication Year, Reference), Cohort and Sample Size	Radiographic Biomarker or Method	Primary Outcome Definition	Study Performance
(Nurmirinta et al. 2025) [9] OAI; 683 participants (1222 knees)	Knee morphology and KL grade; two-stage random forest	KL < 2 classified at follow-up as KL 0–1, KL 2, or KL 3–4/TKR, over 8 years	The combined radiographic–demographic model performed best (weighted F1 78.3%; balanced accuracy 68.2%), compared with radiographic morphology alone (76.5%; 63.8%) and demographics alone (77.2%; 65.6%).

Table 1. *Cont.*

Study (Authors, Publication Year, Reference), Cohort and Sample Size	Radiographic Biomarker or Method	Primary Outcome Definition	Study Performance
(Lee et al. 2025) [10] OAI development: 5966 knees; MOST external validation: 3392 knees	KL and JSN grades (Machine learning: random forest)	Increase in KL 0–2 grades over 4–5 years	The model achieved external-validation AUC 0.76, accuracy 0.68 and F1-score 0.56 in MOST; baseline KL grade, contralateral KOA and lateral JSN were the leading radiographic predictors.
(Janvier et al. 2017) [11] OAI; 1124 participants (1647 knees)	Subchondral tibial TBT using fractal analysis	Increase in JSN and osteophytes over 48 months	Adding baseline TBT improved prediction of incident KL-defined KOA (AUC 0.69), JSN (AUC 0.73) and tibial osteophytes (AUC 0.71), compared with clinical variables alone (AUC 0.57–0.59). Combined-model AUC 0.77 (95% CI 0.73–0.80) versus 0.60 (0.56–0.64) for clinical covariates
(Riddle et al. 2016) [12] MOST development: 1690 participants; OAI external validation: 2422 participants	Baseline KL grade and contralateral KOA; prediction rule	Increase in KL 0–1 to KL ≥ 2 over 4–5 years	The prediction rule achieved AUCs of 0.79 in MOST and 0.81 in external OAI validation; baseline KL grade 1, contralateral KOA, higher BMI and higher WOMAC total score predicted rapid incident KOA.
(Kerkhof et al. 2014) [13] Rotterdam Study I: 2628 participants	Baseline KL grade	Increase in KL 0–1 to KL ≥ 2 over 4–10 years	Adding baseline KL grade to age, sex and BMI increased the AUC from 0.66 (95% CI 0.64–0.70) to 0.79 (95% CI 0.77–0.81); comparable performance was obtained in two external validation cohorts, whereas genetic and biochemical markers provided little additional value
(Shamir et al. 2009) [14] Baltimore Longitudinal Study of Aging; 123 participants	Computer-aided radiographic analysis	Increase in KL 0 to KL ≥ 2 over 20 years	Computer-aided radiographic analysis predicted progression from KL 0 to KL 2 with 62% accuracy and to KL 3 with 72% accuracy; the region adjacent to the tibial spines provided the strongest predictive signal.
(Chen et Or 2023) [15] OAI; 3200 high-risk participants	KL grade, osteophytes and JSN; Auto machine learning (AutoML)	First occurrence of frequent knee symptoms and definite tibial osteophytes (KL ≥ 2) in the same knee over 9 years	AutoML models predicted incident KOA (AUCs 0.78–0.81); weighted ensemble, CatBoost and Extra Trees performed best (AUC 0.81), with radiographic features among the most influential predictors
(Bijen et al. 2018) [16] PROOF cohort; 407 overweight/obese women	Baseline radiographic KL grade 1	Incident clinical and/or radiographic KOA at 2.5 and 6.5 years in knees with baseline KL < 2	KL grade 1 predicted incident radiographic KOA with clinically useful post-test probabilities; although MRI-defined OA was more strongly associated with incidence, radiography was considered sufficient for high-risk selection.

Table 1. *Cont.*

Study (Authors, Publication Year, Reference), Cohort and Sample Size	Radiographic Biomarker or Method	Primary Outcome Definition	Study Performance
(Lau et al. 2025) [17] OAI; 2913 participants	Patellar-shape diffusion model and SynPatNet applied to lateral radiographs	Incident patellofemoral or tibiofemoral radiographic OA within 60 months	Baseline plus synthetic patellar shapes predicted incident patellofemoral OA (AUC 0.909 vs. 0.830 for the baseline-shape CNN), but prediction of tibiofemoral OA was limited (AUC 0.597).
(Mononen et al. 2024) [18] OAI; 683 participants (1213 knees)	X-ray-based finite-element simulation of volumetric cartilage degeneration	Radiographic severity at 8 years, classified by follow-up KL grade in knees with baseline KL < 2	X-ray-based simulated cartilage degeneration discriminated KL 0–1 from KL 3–4/TKR at 8 years (AUC 0.72), compared with AUC 0.68 for the MRI-based model.
(Lazzarini et al., 2017) [19] PROOF cohort; 407 overweight/obese women	Quantitative JSW/joint-space area with ML	Incident medial or lateral JSN and other predefined clinical or structural KOA outcomes over 30 months	ML models combining imaging, clinical, and biochemical variables achieved AUCs >0.70; radiographic joint-space variables contributed to models predicting medial and lateral JSN incidence, with AUCs of approximately 0.74 and 0.73.
(Garriga et al., 2020) [20] Chingford cohort; 649 women (1184 knees)	Baseline KL grade and radiographic morphology	Increase in KL 0–1 to KL ≥ 2 over 4–10 years over approximately 4 years	The internally validated radiographic model achieved an AUC of 0.797 versus 0.692 for the clinical model.
(Kinds et al., 2012) [21] CHECK cohort; 653 participants	Quantitative osteophyte area and JSW	Incident radiographic KOA, defined as KL ≥ 2 over 5 years	Adding quantitative radiographic features increased the AUC from 0.64 to 0.74.
(Joseph et al., 2018) [22] OAI; 641 participants	KL grade within multimodal X-ray–MRI models	Development of moderate/severe KOA: KL3–4, WOMAC pain ≥ 5, or TKR, over 8 years, with baseline KL grades 0–2 *	The radiographic–clinical model achieved a cross-validated AUC of 0.67.
(Woloszynski et al., 2012) [23] OAI; 105 participants (203 knees)	TBT	Increase in medial JSN grade with baseline KL< 2 over 4 years	In knees without pre-existing radiographic KOA, medial and lateral TBT predicted JSN increase with AUCs of 0.75 and 0.72, respectively.

Note: Predictive-performance estimates are reported as provided in the original studies. Because study populations, prediction outcomes, follow-up periods, and validation strategies differ, these estimates should not be interpreted as directly comparable across studies. * Participants had baseline KL grades 0–2, and the composite outcome included radiographic and symptomatic worsening or TKR. The study therefore contributed to the pooled incidence/progression evidence rather than representing pure incident radiographic KOA. Sample sizes and 95% confidence intervals (CIs) are reported when provided in the original publications. Abbreviations: AUC, area under the receiver operating characteristic curve; AutoML, automated machine learning; BMI, body mass index; F1, F1 score; JSN, joint-space narrowing; KL, Kellgren–Lawrence; KOA, knee osteoarthritis; MOST, Multicenter Osteoarthritis Study; OAI, Osteoarthritis Initiative; PI–LL, pelvic incidence–lumbar lordosis; TBT, trabecular bone texture; TKR, total knee replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Characteristics of studies predicting knee osteoarthritis progression.

(Study, Publication Year, Reference), Cohort and Sample Size	Radiographic Biomarker or Method	Primary Outcome Definition	Study Performance
(Rajamohan et al. 2026) [6] OAI development: 2248; and MOST external validation: 1189	Deep learning radiographic features (attention-based ResNet-34 with KL-grade pretraining)	Increase in KL grade or total knee replacement over four years among knees with baseline KL grades 2–3.	In MOST, KL-grade diagnostic pretraining improved external KOA prediction compared with ImageNet pretraining (AUC 0.770 vs. 0.747), while experience replay preserved diagnostic performance.
(Sun et al. 2026) [7] FNIH/OAI; 450 participants	Subchondral-bone X-ray radiomics nomogram	Sustained WOMAC pain increase ≥9/100 over 24–48 months	X-ray radiomics combined with clinical factors predicted pain progression (AUC 0.753 (95% CI 0.722–0.809)–0.766 (95% CI 0.708–0.797)).
(Lee et al. 2025) [10] OAI development: 5966 knees; MOST external validation: 3392 knees	KL and JSN grades (Machine learning: random forest)	KL-grade progression over 4–5 years in knees with baseline KL grades 0–2 *	The externally validated model predicted KL-grade progression in MOST (AUC 0.76)
(Salis et al. 2024) [24] OAI development: 3114 participants; OAI validation: 606; MOST external validation: 1602	Semiquantitative X-ray features within an ML risk model	Onset of end-stage KOA within 2–2.5 or 4–5 years, defined by combined radiographic severity and persistent/intense symptoms	The externally validated models predicted end-stage KOA (AUC 0.807 (95% CI 0.811–0.882)–0.853 (0.823–0.881) in MOST).
(Li et al. 2024) [25] FNIH/OAI; 600 participants (one index knee each)	Contralateral-knee osteophytes and JSN (logistic-regression nomogram)	Medial minimum JSW loss ≥ 0.7 mm over 24–48 months	The multimodal nomogram predicted radiographic progression (AUC 0.77); adding 24-month changes produced an AUC of 0.78.
(Almhdie-Imjabbar et al. 2022) [26] OAI; 1888 participants; MOST: 683 participants	Subchondral tibial TBT using fractal analysis and Siamese neural network -estimated KL grade	Increase in medial OARSI JSN grade over 48 months in OAI or 60 months in MOST	The combined TBT–CNN model predicted medial JSN progression (AUC 0.73–0.75 in OAI and 0.78–0.81 in MOST).
(Almhdie-Imjabbar et al. 2023) [27] OAI; 1352 participants	Baseline and 24-month TBT changes	Increase in medial OARSI JSN grade between 24 and 48 months	Adding baseline and 24-month TBT changes improved medial JSN progression prediction (AUC 0.739 (95% CI 0.695–0.782) vs. 0.676; $p = 0.008$).
(Almhdie-Imjabbar et al. 2024) [28] FNIH/OAI; 600 participants (597 analyzed)	Baseline and 24-month TBT changes	Concurrent medial minJSW loss ≥ 0.7 mm and sustained WOMAC pain increase ≥9/100 over 24–48 months	TBT-change models predicted radio-symptomatic, radiographic, and symptomatic progression with AUCs of 0.658 (95% CI 0.612–0.705), 0.752 (95% CI 0.700–0.804), and 0.698 (95% CI 0.641–0.756), respectively.
(Chen et al. 2023) [15] OAI; 3200 participants	AutoML using multimodal OAI variables; radiographic predictors included KL/composite OA grade, osteophytes, and JSN	Increase in knee pain and functional decline, assessed longitudinally using WOMAC pain and physical-function scores over 9 years	Weighted-ensemble and CatBoost models predicted knee pain progression (mean RMSE 2.27–2.30) and functional decline (mean RMSE 7.01–7.33).
(Tiulpin et al. 2019) [29] OAI; 2711 participants (4928 knees); MOST: 2129 participants (3918 knees)	Raw radiographic features using a multitask CNN–GBM model	Any KL-grade increase—excluding KL 0→1—or total knee replacement within 7 years	CNN and clinical-data fusion externally predicted KOA progression in MOST (AUC 0.79); adding baseline KL grade increased the AUC to 0.81 (95% CI 0.79–0.82).

Table 2. *Cont.*

(Study, Publication Year, Reference), Cohort and Sample Size	Radiographic Biomarker or Method	Primary Outcome Definition	Study Performance
(Halilaj et al. 2018) [30] OAI: 1243 participants	Baseline and 1-year bilateral JSW changes	Membership in a progressing JSW trajectory over eight years, identified using mixture modelling	One-year bilateral JSW measurements predicted eight-year radiographic progression with an AUC >0.86, whereas baseline-only prediction had an AUC <0.60.
(Kraus et al. 2018) [31] FNIH/OAI; 600 participants	Medial tibial TBT using fractal signature analysis	Concurrent medial minJSW loss ≥ 0.7 mm and sustained WOMAC pain increase ≥9/100 over 2–4 years	TBT composites modestly improved radio-symptomatic progression prediction over covariates alone C-statistic 95% CIs were reported for individual models; the principal range was 0.633–0.649 versus 0.608 for covariates alone.
(Janvier et al. 2017) [32] OAI; 1124 participants	Subchondral tibial TBT using fractal analysis	Increase in OARSI JSN grade over 48 months	TBT predicted JSN progression (AUC up to 0.71); combining TBT, baseline JSN, and clinical variables increased the AUC to 0.77 (95% CI 0.73–0.80).
(Woloszynski et al. 2012) [33] OAI; 50 participants	Tibial TBT analysis	Increase in medial JSN grade over 4 years	Medial TBT predicted JSN progression in knees with and without baseline radiographic OA (AUC 0.77 and 0.75, respectively).
(Woloszynski et al. 2012) [23] OAI; 105 participants	Tibial TBT–based DMC system	Increase in medial JSN grade over 4 years	The DMC system predicted OA progression with 80% accuracy, 77.97% sensitivity and 82.00% specificity
(Kraus et al. 2009) [34] Prediction of Osteoarthritis Progression study: 138 participants (248 knees)	Subchondral TBT/FSA	Increase in JSN/osteophyte over 3 years	Baseline medial tibial FSA predicted medial JSN progression (AUC 0.75); combining FSA with alignment and clinical variables increased AUC to 0.79
(Mazzuca et al. 2005) [35] Clinical-trial cohort; 159 obese women	KL grade plus WOMAC pain	Medial JSW loss ≥ 0.50 mm within 16–30 months	KL grade 3 combined with above-median pain predicted progression with 65% sensitivity, 79% specificity, PPV 48% and NPV 88%, outperforming bone scintigraphy
(Yoshikawa et al. 2026) [36] MOST; 302 participants (425 knees)	Baseline radiographic 2D JSW compared with WBCT-derived 3D JSW	Increase in tibiofemoral OARSI JSN grade over 24 months	Radiographic 2D JSW predicted medial JSN worsening (AUC 0.711 which was 0.085 higher (95% CI −0.163–−0.008, $p = 0.032$) vs. 0.626 for demographics) and showed high discrimination for lateral JSN worsening (AUC 0.893 which was 0.089 higher (95% CI −0.187–0.008, $p = 0.073$)); WBCT-derived 3D JSW was not superior.
(Yoshikawa et al. 2026 [37] MOST; 302 participants (425 knees)	Baseline radiographic 2D JSW compared with WBCT-derived 3D JSW	Minimal clinically important worsening of WOMAC pain, WOMAC function, 20 m walk, or sit-to-stand performance over 24 months	Radiographic 2D JSW showed limited prediction of symptomatic or functional worsening (WOMAC pain AUC 0.511); WBCT-derived 3D JSW did not significantly outperform radiography.

Table 2. *Cont.*

(Study, Publication Year, Reference), Cohort and Sample Size	Radiographic Biomarker or Method	Primary Outcome Definition	Study Performance
(Panfilov et al. 2025) [38] OAI: 2421 participants (3967 knees)	Deep X-ray features within a multimodal transformer combining radiographs and structural/compositional MRI	Radiographic KOA progression over prediction horizons of 1–8 years	Multimodal fusion performed best for 1-year progression (AUC 0.76); structural MRI and multimodal approaches achieved AUCs of 0.70–0.76 over 2–8 years.
(Castagno et al. 2025) [39] FNIH/OAI; 600 participants; POMA study: 987	X-ray features within multimodal AutoML models	Rapid radiographic and/or pain progression over 2 years	Multimodal AutoML predicted rapid progression; externally validated clinical-only models achieved AUC-PRC 0.727 (95% CI 0.726–0.728) for multiclass and 0.764 (0.762–0.766) for binary outcomes, while multiclass performance was strongest in early-stage OA (AUC-PRC 0.724–0.806).
(Hunter et al. 2022) [40] FNIH/OAI; 600 participants	Radiographic TBT within multimodal imaging and biochemical models	Concurrent radiographic and pain progression, with radiographic progression assessed separately, over 24–48 months	Multimodal models achieved C-statistics of 0.641–0.671 using baseline biomarkers and 0.680–0.724 using 24-month changes; models for radiographic progression alone reached 0.716–0.832.
(Attur et al. 2020) [41] NYU clinical cohort and OAI replication cohort; 473 participants overall	Radiographic osteophyte score within a multimodal biomarker model	Medial JSW loss ≥ 0.5 mm over 24 months	Combining inflammatory gene expression with MRI bone-marrow lesions increased the AUC from 0.66 to 0.75; adding the radiographic osteophyte score further improved prediction of medial JSN.
(Jamshidi et al. 2020) [42] OAI: 1590 participants	Radiographic JSW and JSN within machine learning feature-selection models	KL grade ≥ 2 or medial JSN grade ≥1 at 48 months	Multilayer-perceptron models predicted KL- and JSN-defined structural progression with AUCs of 0.88 and 0.95, respectively; baseline JSW and JSN were among the leading predictors.
(Kraus et al. 2013) [43] Pfizer A9001140 observational cohort; 60 women	Radiographic subchondral bone trabecular integrity using FSA	At least 5% change in medial JSW or joint-space area over 24 months	Baseline trabecular integrity predicted 24-month radiographic progression, with AUCs of 0.81 for JSW loss and 0.85 for joint-space-area change.
(Guan et al., 2020) [44] OAI: 1800 participants	Radiographic deep learning	Medial JSW loss ≥ 0.7 mm over 48 months	The baseline-radiograph DL model achieved an AUC of 0.799, compared with 0.660 for the conventional risk-factor model. The combined model achieved an AUC of 0.863 (95% CI 0.825–0.895), with 80.5% sensitivity and specificity.
(Joseph et al., 2018) [22] OAI: 641 participants	KL grade within multimodal prediction models	Composite moderate/severe KOA outcome over 8 years, with baseline KL grades 0–2 *	The KL-based radiographic–clinical model achieved AUC 0.67; MRI features provided modest incremental improvement, with a maximum AUC of 0.72.

Table 2. *Cont.*

(Study, Publication Year, Reference), Cohort and Sample Size	Radiographic Biomarker or Method	Primary Outcome Definition	Study Performance
(Woloszynski et al., 2012) [23] OAI: 105 participants	TBT	Increase in medial JSN grade with baseline KL ≥ 2 over 4 years	In knees with pre-existing OA, medial and lateral TBT achieved AUCs of 0.77 and 0.71, respectively; corresponding values in knees without pre-existing OA were 0.75 and 0.72.

Note: Predictive-performance estimates are reported as provided in the original studies. Because study populations, prediction outcomes, follow-up periods, and validation strategies differ, these estimates should not be interpreted as directly comparable across studies. * Because the population included baseline KL0–2 knees, the pooled outcome encompassed both incident and progressive radiographic KOA; separate performance estimates were not reported for these subgroups. Sample sizes and 95% confidence intervals (CIs) are reported when provided in the original publications. Abbreviations: AUC, area under the receiver operating characteristic curve; AutoML, automated machine learning; CNN, convolutional neural network; DMC, dissimilarity-based multiple classifier; FSA, fractal signature analysis; GBM, gradient boosting machine; ICC, intraclass correlation coefficient; JSN, joint-space narrowing; JSW, joint-space width; KL, Kellgren–Lawrence; KOA, knee osteoarthritis; MAE, mean absolute error; minJSW, minimum joint-space width; ML, machine learning; MOST, Multicenter Osteoarthritis Study; NPV, negative predictive value; OA, osteoarthritis; OAI, Osteoarthritis Initiative; OARSI, Osteoarthritis Research Society International; PPV, positive predictive value; ResNet, residual neural network; RMSE, root mean square error; TBT, trabecular bone texture; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; NYU, New York University study; POMA, Pivotal Osteoarthritis Initiative MRI Analyses study.

2.6. Classification of Radiographic Biomarkers and Analytical Methods

To facilitate clinical interpretation, the evaluated radiographic biomarkers and analytical approaches were grouped into four broad, potentially overlapping categories:

- Conventional radiographic measures: KL grade, JSN grade, osteophytes, minimum or compartment-specific JSW, and longitudinal JSW change.
- Geometric and biomechanical radiographic measures: bone and joint morphology, knee shape, spinopelvic parameters, and lower-limb or compartment-specific alignment.
- Subchondral bone-texture biomarkers: TBT and FSA derived from predefined tibial or subchondral regions of interest.
- Computational image-analysis approaches: computer-aided image analysis, radiomics, random forests, gradient-boosting methods, automated machine learning, convolutional neural networks, deep learning, and multimodal models integrating radiographic and clinical variables.

These categories were not considered mutually exclusive. For example, TBT could be integrated into a deep learning model, while conventional KL or JSN grades could be incorporated into machine learning and multimodal prediction models.

2.7. Evidence Synthesis

The evidence was synthesized qualitatively according to the clinical prediction objective. Incidence studies and progression studies were analyzed separately because of differences in baseline radiographic status, outcome definitions, and intended clinical application. Studies addressing both outcomes contributed to both syntheses.

Within each prediction objective, studies were grouped according to biomarker category, outcome definition, prediction horizon, analytical method, validation strategy, and reported performance. Particular attention was given to whether advanced imaging biomarkers provided additional predictive information beyond conventional radiographic and clinical variables and whether model performance was evaluated in an independent cohort.

A quantitative meta-analysis was not undertaken because of substantial heterogeneity in study populations, baseline KL grades, radiographic acquisition and processing, biomarker definitions, prediction horizons, outcomes, modelling strategies, and performance measures. Evidence maturity and potential clinical applicability were therefore assessed qualitatively by considering the consistency of findings, interpretability, methodological standardization, availability of external validation, and feasibility of implementation in clinical practice. Accordingly, reported AUC values were interpreted within the context of each study rather than used to establish a direct performance ranking across different biomarker categories or modelling approaches.

3. Results

3.1. Study Selection

The initial literature search identified 242 potentially relevant records. After duplicate removal and title and abstract screening, 88 articles underwent full-text assessment. Of these, 24 studies met the predefined eligibility criteria and were included in the qualitative synthesis.

Because the initial search strategy contained exclusion terms related to MRI, computed tomography, ultrasound, and surgery, supplementary sensitivity searches were conducted without these restrictive exclusion blocks. The imaging-focused supplementary search retrieved 112 records. After removing records already identified by the initial search and screening the remaining records according to the same eligibility criteria, 11 additional eligible studies were identified. These studies evaluated conventional radiographic predictors either independently or within multimodal prediction models.

Citation searching and structured reassessment of the studies included in our previous 2023 review were also undertaken to ensure coverage of the earlier evidence base. Although their full texts had been assessed previously, all potentially relevant studies were re-evaluated according to the eligibility criteria of the present review. Five additional eligible studies were identified through this process. Following final application of the eligibility criteria across all search sources, 38 unique studies were included in the qualitative synthesis (Figure 1).

The principal reasons for exclusion were publication type or language restrictions, including conference abstracts, review articles, editorials, and non-English-language publications; the absence of a longitudinal prediction or prognostic assessment, including diagnostic, descriptive, cross-sectional, genetic, and synthetic-image studies [45,46]; the use of non-radiographic predictors or outcomes outside the scope of the review, including physical-activity, biochemical, DXA-derived, MRI-derived, biomechanical, scintigraphic, or extra-articular measures [47–49]; an outcome that did not meet the predefined definition of incident or progressive KOA; and longitudinal risk-factor or association analyses that did not develop or validate a prediction model or report measures of predictive performance [5,50–58]. Studies using MRI, computed tomography, biochemical, clinical, or other non-radiographic data were not excluded when at least one eligible conventional radiographic predictor contributed to the prediction model.

Overall, the final dataset provides a focused synthesis of longitudinal studies evaluating radiographic biomarkers for KOA prediction, including multimodal studies in which conventional radiographic predictors contributed to the prediction model.

3.2. Characteristics of Included Studies

The 38 included studies were published between 2005 and 2026 and varied considerably in population characteristics, follow-up duration, radiographic biomarkers, prediction methods, and outcome definitions (Tables 1 and 2). Most studies used data from large longitudinal cohorts, particularly the Osteoarthritis Initiative (OAI) and the Multicenter

Osteoarthritis Study (MOST), whereas others relied on population-based or institution-specific cohorts. Follow-up periods ranged from approximately 16 months to 28 years, although most prediction intervals were between two and eight years.

The radiographic predictors ranged from conventional semiquantitative and quantitative measurements—including Kellgren–Lawrence (KL) grade, joint-space narrowing (JSN), joint-space width (JSW), osteophytes, and lower-limb alignment—to more advanced image-derived biomarkers, such as subchondral trabecular bone texture (TBT), fractal signature analysis (FSA), radiomic features, knee morphology, patellar shape, finite-element-derived features, and deep learning representations extracted directly from radiographs. Analytical approaches also evolved over time, progressing from conventional regression models and clinical prediction rules to random forests, gradient-boosting methods, automated machine learning, convolutional neural networks (CNNs), and multimodal models integrating radiographic features with clinical, biochemical, MRI, or weight-bearing computed tomography data.

Outcome definitions were heterogeneous. Incident radiographic KOA was generally defined as progression from a baseline KL grade of 0 or 1 to KL $\geq$ 2. However, some studies used increases in individual radiographic features, including JSN or osteophytes, or combined radiographic abnormalities with frequent knee symptoms. Other incidence outcomes included the onset of patellofemoral or tibiofemoral OA and longer-term radiographic severity in knees without definite KOA at baseline.

Progression outcomes included increases in KL or OARSI JSN grades, quantitative JSW loss prediction of future continuous JSW values, development of radiographic end-stage KOA, development of end-stage KOA, persistent worsening of knee pain, and composite radio-symptomatic outcomes. Total knee replacement alone was not considered an eligible progression outcome, although studies using a composite advanced-disease outcome were retained when the outcome also incorporated an eligible radiographic component.

Predictive performance was most frequently reported using the area under the receiver operating characteristic curve (AUC), although the area under the precision–recall curve (AUC-PRC), accuracy, sensitivity, specificity, positive and negative predictive values, F1-score, balanced accuracy, mean absolute error, root mean squared error, calibration measures, and intraclass correlation coefficients were also reported. In multimodal studies, performance was interpreted as reflecting the complete predictor set unless the independent or incremental contribution of the conventional radiographic component was specifically evaluated.

3.3. Classification According to the Clinical Prediction Objective

The included studies were classified according to whether their principal objective was to predict KOA incidence, KOA progression, or both outcomes. Of the 38 unique studies, eleven investigated incidence only, 23 progression only, and four both objectives or evaluated a pooled outcome encompassing incident and progressive disease. Accordingly, 15 studies contributed to the incidence synthesis and 27 to the progression synthesis. Studies addressing both outcomes were represented in both evidence tables but counted only once in the total evidence base.

Most investigations focused on progressive KOA, reflecting the long-standing use of radiographic biomarkers to predict structural deterioration in patients with established disease. A smaller but increasingly important group of studies evaluated incident KOA, aiming to identify structural alterations preceding the development of definite radiographic disease in knees with baseline KL grades of 0–1. Two studies assessed both incidence and progression, particularly using quantitative or computational radiographic approaches. The supplementary sensitivity search expanded both categories by identifying multimodal studies in which conventional radiographic predictors were evaluated alongside MRI,

weight-bearing computed tomography, biochemical biomarkers, clinical variables, or patient-reported outcomes.

Incidence-prediction studies generally included knees without definite radiographic KOA at baseline and assessed their subsequent progression to KL grade ≥ 2 or another predefined incidence outcome. In contrast, progression-prediction studies included knees with existing radiographic or symptomatic abnormalities and evaluated subsequent structural, symptomatic, or combined disease worsening. This distinction between incident and progressive KOA constitutes a central conceptual framework of the present review, as the predictive value of individual radiographic biomarkers appears to depend on the baseline disease stage and the intended clinical prediction objective. Morphological characteristics and early semiquantitative radiographic features were investigated for incidence prediction, while TBT/FSA contributed to both incidence and progression prediction. KL grade, JSN, quantitative JSW, osteophytes, radiomics, and multimodal AI models were more frequently investigated in relation to progression.

3.4. Prediction of Knee Osteoarthritis Incidence

Radiographic biomarkers for predicting incident KOA primarily targeted knees without definite radiographic osteoarthritis at baseline, most commonly those with KL grades of 0–1. The included studies investigated conventional radiographic grading, quantitative JSW and osteophyte measurements, bone and joint morphology, patellar shape, alignment, subchondral TBT, finite-element-derived features, and computational features extracted using machine learning or computer-aided approaches. Collectively, these studies indicate that conventional radiographs contain predictive information before the development of definite radiographic KOA; however, the relative performance of individual biomarkers varied according to the population, outcome definition, and prediction model.

Conventional radiographic severity at baseline remained an important predictor of incident KOA. Adding baseline KL grade to age, sex, and BMI increased the AUC from 0.66 to 0.79, with comparable performance in two external validation cohorts [13]. Similarly, the prediction rule developed by Riddle et al., which incorporated baseline KL grade, contralateral KOA, BMI, and WOMAC score, achieved AUCs of 0.79 in MOST and 0.81 in the external OAI validation cohort [12]. A random-forest model incorporating KL and JSN grades achieved an external-validation AUC of 0.76, with baseline KL grade, contralateral KOA, and lateral JSN among the leading predictors [10]. Conventional radiographic features contributed predictive information when combined with clinical and contralateral-knee variables.

The predictive value of minor baseline radiographic abnormalities was also evaluated in overweight and obese women without definite KOA. Baseline KL grade 1 predicted incident clinical and radiographic KOA at 2.5 and 6.5 years, with clinically informative post-test probabilities [36]. Although MRI-defined tibiofemoral OA was more strongly associated with subsequent incidence, the greater prevalence and accessibility of KL grade 1 supported the practical value of conventional radiography for selecting individuals at increased risk.

Quantitative assessment of individual radiographic features provided additional predictive information beyond conventional grading. In participants with recent-onset knee pain from the CHECK cohort, the addition of osteophyte area and minimum JSW to demographic and clinical variables increased the AUC for incident KL-defined KOA from 0.64 to 0.74; quantitative radiographic features also performed slightly better than KL grading alone [21]. In the Chingford cohort, an internally validated radiographic model incorporating baseline KL grade 1, contralateral radiographic KOA and other structural variables achieved an AUC of 0.797, compared with 0.692 for a model based on clinical and biochemical variables [20]. Machine learning models combining quantitative joint-space information

with clinical and biochemical variables also achieved AUCs above 0.70 for several 30-month incidence outcomes among overweight and obese women without KOA at baseline [19]. Together, these results indicate that minor semiquantitative abnormalities and separate quantitative radiographic features may improve incidence prediction before definite KOA becomes apparent.

Quantitative analysis of bone morphology and alignment provided additional approaches for detecting early structural susceptibility. Nurmirinta et al. combined knee morphology and KL grade with demographic variables in a two-stage random-forest model [9]. The combined model achieved a weighted F1-score of 78.3% and balanced accuracy of 68.2%, outperforming models based on radiographic morphology or demographic variables alone. These results suggest that morphological and alignment-related features may complement established demographic and radiographic risk factors, although the available evidence does not establish their consistent superiority over conventional KL grading.

Subchondral TBT was also evaluated as an early imaging biomarker. Janvier et al. found that adding baseline tibial TBT to clinical variables improved the prediction of incident KL-defined KOA, JSN, and tibial osteophyte formation, producing AUCs of 0.69, 0.73, and 0.71, respectively, compared with 0.57–0.59 for clinical variables alone [11]. In another longitudinal cohort, medial and lateral TBT predicted subsequent JSN increase among knees without pre-existing radiographic KOA, with AUCs of 0.75 and 0.72, respectively [23]. These findings support the hypothesis that alterations in subchondral trabecular architecture may precede definite radiographic disease. Nevertheless, differences in cohort characteristics, texture-analysis methods, radiographic acquisition, and incidence definitions indicate that further independent and externally validated prediction studies remain necessary before TBT can be adopted as a standalone incidence-prediction biomarker.

More recently, computer-aided analysis and artificial intelligence have expanded the quantitative information obtainable from conventional radiographs. Computer-derived radiographic features predicted progression from KL grade 0 to KL grade 2 with 62% accuracy and to KL grade 3 with 72% accuracy; the region adjacent to the tibial spines provided the strongest predictive signal [14]. Chen et al. subsequently reported AUCs of 0.78–0.81 for automated machine learning models predicting incident symptomatic KOA, with weighted-ensemble, CatBoost, and Extra-Trees models achieving the highest discrimination [15]. These approaches can extract quantitative radiographic patterns that may not be readily identifiable through visual assessment, although external prospective validation remains necessary.

Patellar morphology was subsequently evaluated using a generative diffusion model applied to lateral knee radiographs. Combining baseline and synthetically generated follow-up patellar shapes improved prediction of incident patellofemoral OA within 60 months, with an AUC of 0.909 compared with 0.830 for a CNN using baseline shape alone [17]. In contrast, prediction of tibiofemoral OA remained limited (AUC 0.597), indicating that the prognostic value of shape-based biomarkers may be compartment-specific.

An X-ray-based finite-element workflow provided an additional computational approach to early risk prediction. Radiographic and MRI measurements were separately used to construct finite-element models generating simulated volumes of cartilage degeneration. These simulated quantities were evaluated against observed KL grade at eight years. The X-ray-based model discriminated knees remaining at KL grades 0–1 from those reaching KL grades 3–4 or total knee replacement with an AUC of 0.72, compared with 0.68 for the MRI-based model [18]. Importantly, cartilage degeneration was simulated rather than measured longitudinally, and the outcome reflected longer-term radiographic severity rather than a pure binary incidence definition.

In the TOARP study, a model combining baseline KL grade with clinical variables achieved a cross-validated AUC of 0.67 for predicting moderate-to-severe KOA over eight years. The addition of MRI-derived morphology and cartilage T2 increased the AUC to 0.71 and 0.72, respectively [22]. This finding illustrates the potential incremental value of multimodal imaging, while also showing that relevant predictive information was already available from conventional radiographic and clinical variables. Because baseline KL grades ranged from 0 to 2 and the composite outcome comprised KL3–4, WOMAC pain ≥5, or total knee replacement, the study represents pooled disease development and progression rather than pure radiographic incidence.

Broader multimodal prediction was evaluated in participants with baseline KL grades 0–2 and minimal symptoms. A model combining baseline KL grade with demographic and clinical variables predicted the development of moderate-to-severe KOA over eight years with a cross-validated AUC of 0.67. Adding MRI-defined morphological abnormalities increased the AUC to 0.71, while the further addition of cartilage T2 produced an AUC of 0.72 [22]. Because the study included baseline KL0–2 knees and used a composite endpoint comprising KL3–4, WOMAC pain ≥5, or total knee replacement, it reflects pooled disease development and progression rather than pure radiographic incidence. Nevertheless, it illustrates both the predictive information available from baseline conventional radiography and the modest incremental contribution of MRI-derived features.

Overall, incidence-prediction studies evaluated baseline KL grade, quantitative JSW and osteophyte measurements, bone morphology and alignment, TBT/FSA, patellar shape, finite-element-derived features, and AI-derived radiographic features, frequently in combination with clinical variables. Predictive information was reported for both conventional radiographic–clinical models and advanced quantitative approaches, but no biomarker category consistently outperformed the others. Differences in study populations, outcome definitions, prediction horizons, and validation strategies limited direct comparisons across studies.

3.5. Prediction of Knee Osteoarthritis Progression

Studies investigating KOA progression predominantly included knees with early or established radiographic disease, generally within baseline KL grades 1–3. Progression was defined using increases in KL or OARSI JSN grade, quantitative JSW loss, prediction of future JSW values, development of end-stage KOA, sustained pain worsening, or combined radio-symptomatic outcomes. Follow-up periods generally ranged from two to eight years, although shorter prediction horizons were also evaluated.

Conventional radiographic biomarkers, particularly KL grade, JSW, and JSN, remained central to structural-progression prediction. An externally validated random-forest model incorporating KL and JSN grades achieved an AUC of 0.76 [10]. When semiquantitative radiographic features were combined with clinical variables, end-stage KOA was predicted with AUCs of 0.807–0.853 in MOST [24]. Contralateral-knee osteophytes and JSN were also incorporated into a nomogram predicting medial JSW loss, with an AUC of 0.77, increasing to 0.78 after the addition of 24-month changes [25]. In another study, the combination of KL grade 3 and above-median WOMAC pain predicted JSW loss with 65% sensitivity, 79% specificity, a positive predictive value of 48%, and a negative predictive value of 88% [35].

The prognostic value of radiographic JSW was further supported by comparative studies involving weight-bearing computed tomography. Baseline radiographic 2D-JSW predicted 24-month medial JSN worsening with an AUC of 0.711, compared with 0.626 for a demographic model, and showed high discrimination for lateral JSN worsening (AUC 0.893) [36]. Weight-bearing CT-derived 3D-JSW did not significantly outperform radiographic 2D-JSW. For symptomatic and functional outcomes, however, both approaches showed limited discrimination: radiographic 2D-JSW produced an AUC of 0.511 for

WOMAC pain worsening, and 3D-JSW provided no significant improvement [37]. These findings reinforce the distinction between predicting structural deterioration and predicting clinical worsening.

Longitudinal JSW measurements provided particularly strong prognostic information. The combination of baseline and one-year bilateral JSW measurements predicted membership in an eight-year progressing trajectory with an AUC greater than 0.86, whereas baseline measurements alone produced an AUC below 0.60 [30]. These results suggest that longitudinal quantitative assessment captures progression-related information that may not be fully represented by a single baseline radiographic grade.

Lower-limb alignment was less extensively investigated in the final set of progression studies. Nevertheless, its potential biomechanical contribution was demonstrated when alignment and clinical variables were added to fractal signature analysis, increasing the AUC for medial JSN progression from 0.75 to 0.79 [34]. Alignment may therefore provide complementary compartment-specific prognostic information, although its incremental contribution requires further evaluation in dedicated prediction models.

TBT was the most frequently investigated quantitative radiographic biomarker for structural progression. TBT-based approaches predicted JSN progression with AUCs ranging from 0.71 to 0.77, while combining TBT with baseline JSN, alignment, or clinical variables increased the AUC to 0.77–0.79 [23,32,34]. A TBT-based multiple-classifier system achieved 80% accuracy, 77.97% sensitivity, and 82.00% specificity [33]. Baseline radiographic trabecular integrity also predicted a ≥5% change in JSW and joint-space area over 24 months, with AUCs of 0.81 and 0.85, respectively [43]. More modest improvements were observed for radio-symptomatic progression, for which TBT composites increased the C-statistic from 0.608 for covariates alone to 0.633–0.649 [31].

The integration of TBT with deep learning and longitudinal measurements provided additional predictive information. A combined TBT–CNN model predicted medial JSN progression with AUCs of 0.73–0.75 in the OAI and 0.78–0.81 in MOST [26]. The addition of baseline and 24-month TBT changes significantly improved prediction relative to a reference model (AUC 0.739 versus 0.676; \($p = 0.008$\)) [27]. TBT changes also predicted radiographic, symptomatic, and combined radio-symptomatic progression, with AUCs of 0.752, 0.698, and 0.658, respectively [28]. Alongside its reported predictive value for incident KOA [11], these findings suggest that TBT captures subchondral bone alterations across different stages of KOA development.

Multimodal biomarker studies examined whether radiographic predictors could contribute additional information when integrated with MRI, biochemical, or clinical variables. A radiographic osteophyte score, combined with inflammatory gene expression and MRI-defined bone-marrow lesions, improved prediction of medial JSW loss; adding MRI bone-marrow lesions increased the AUC from 0.66 to 0.75, with further improvement after addition of the osteophyte score [41].

In the FNIH OA Biomarkers Consortium, radiographic TBT contributed to multivariable imaging and biochemical models. C-statistics ranged from 0.641 to 0.671 for baseline-biomarker models and from 0.680 to 0.724 when 24-month changes were incorporated, while models predicting radiographic progression alone reached 0.716–0.832 [40]. These performance estimates reflect the integrated biomarker sets and should not be attributed exclusively to their radiographic components.

Artificial-intelligence models enabled radiographic features to be extracted directly and combined with conventional imaging or clinical variables. KL-grade diagnostic pretraining improved external prediction of structural progression in MOST compared with ImageNet pretraining (AUC 0.770 versus 0.747), while experience replay preserved diagnostic performance [6]. Similarly, the combination of CNN-derived radiographic features

and clinical variables achieved an externally validated AUC of 0.79, increasing to 0.81 after baseline KL grade was added [29]. Machine learning feature-selection models incorporating radiographic JSW and JSN predicted KL- and JSN-defined structural progression with AUCs of 0.88 and 0.95, respectively [42]. In addition, a DL model based on baseline radiographs predicted medial JSW loss ≥ 0.7 mm over 48 months with an AUC of 0.799, compared with 0.660 for a conventional model based on demographic and radiographic risk factors. Combining the image-derived representation with these conventional risk factors increased the AUC to 0.863 [44]. This finding indicates that DL can extract complementary progression-related information from baseline radiographs; however, validation was performed using a hold-out subset of the same OAI source population rather than a fully independent cohort.

Multimodal models further evaluated whether MRI-derived features provided additional information beyond conventional radiographic and clinical predictors. In the TOARP study, the addition of MRI morphology and cartilage T2 to a model incorporating baseline KL grade and clinical variables increased the cross-validated AUC from 0.67 to 0.72 [22]. Because its baseline population included KL0–2 knees and its composite outcome encompassed KL3–4, substantial pain, or total knee replacement, the study reflects pooled disease development and progression rather than progression of established radiographic KOA alone. Transformer-based multimodal fusion of radiographs with structural and compositional MRI achieved an AUC of 0.76 for one-year radiographic progression [38]. For prediction horizons of two to eight years, structural MRI and multimodal approaches produced AUCs of 0.70–0.76. Although these findings support integration of radiographic and MRI information, they do not demonstrate that the radiographic component independently accounted for the overall performance.

AutoML models integrating clinical, biochemical, X-ray, and MRI data also predicted rapid radiographic and/or pain progression over two years [39]. Externally validated clinical-only models achieved AUC-PRC values of 0.727 for multiclass and 0.764 for binary outcomes, while multiclass performance was strongest in early-stage OA (AUC-PRC 0.724–0.806). Patient-reported and MRI variables emerged as important predictors, indicating that the findings support radiographs as components of multimodal prediction rather than demonstrating the superiority of X-ray-based features alone.

Radiographic biomarkers were also applied to symptomatic outcomes. Sustained WOMAC pain worsening was predicted using subchondral-bone radiomics combined with clinical factors, with AUCs of 0.753–0.766 [7]. Automated machine learning was additionally used to predict pain progression, functional decline, and incident KOA [15]. However, the limited performance of baseline JSW for predicting WOMAC pain and functional worsening illustrates that structural and symptomatic progression represent related but non-interchangeable prediction objectives [37].

Across progression studies, KL grade, JSN, quantitative JSW, alignment, TBT/FSA, radiomics, and AI-derived features were evaluated against structural, symptomatic, or composite outcomes. Reported predictive performance varied according to the study population, baseline disease severity, prediction horizon, outcome definition, predictor set, and validation strategy. Accordingly, AUC values were treated as study-specific estimates and were not used to rank biomarker categories directly. No advanced biomarker demonstrated consistent superiority over conventional or longitudinal quantitative radiographic measures across independent cohorts.

4. Discussion

4.1. Principal Findings

This narrative review synthesized 38 unique longitudinal studies evaluating biomarkers derived from conventional knee radiographs for predicting incident or progressive knee osteoarthritis (KOA). Eleven studies addressed incidence only, 23 addressed progression only, and four evaluated both outcomes. The available evidence indicates that the prognostic information obtainable from conventional radiographs depends substantially on baseline disease stage, the outcome definition, and the prediction horizon. No single biomarker was consistently superior across all clinical contexts. Instead, the findings support the complementary use of conventional radiographic measures, quantitative image-derived biomarkers, and computational approaches.

In knees without definite radiographic KOA, minor conventional abnormalities already conveyed relevant prognostic information. In the Rotterdam Study I, baseline Kellgren–Lawrence (KL) grade substantially improved prediction of incident KOA beyond age, sex, and body mass index (BMI), with comparable findings obtained through external validation in the Rotterdam Study II and Chingford Study cohorts [13]. Similarly, a prediction model developed in the Multicenter Osteoarthritis Study (MOST), incorporating baseline KL grade 1, contralateral KOA, BMI, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score, demonstrated reproducible discrimination when externally validated in the Osteoarthritis Initiative (OAI) [12].

Quantitative morphology, trabecular bone texture (TBT), fractal signature analysis (FSA), and computational image analysis provided complementary information for early prediction. A model combining radiographic knee morphology with demographic variables performed better than models based on either source alone [9]. Baseline TBT improved prediction of incident KL-defined KOA, joint-space narrowing (JSN), and tibial osteophyte formation [11]. In addition, short-term variations in TBT parameters, combined with radiographic and clinical biomarkers, improved prediction of subsequent radiographic KOA progression compared with baseline predictors alone [27]. Computer-aided image analysis also identified subtle radiographic patterns associated with the development of KOA over long-term follow-up [14]. Nevertheless, the incremental value of these quantitative approaches varied according to the population, endpoint, and analytical method. Their current role should therefore be regarded as complementary rather than as a replacement for conventional assessment.

For progressive KOA, measures of existing structural damage remained highly informative. KL grade, JSN, quantitative joint-space width (JSW), and early longitudinal changes in JSW were repeatedly incorporated into predictive models. One-year bilateral JSW changes predicted subsequent membership in an eight-year progressing trajectory more effectively than models based exclusively on baseline measurements had substantially lower discrimination [30]. This finding emphasizes that short-term structural change may sometimes provide greater prognostic information than a single baseline examination.

TBT/FSA was evaluated across both incidence and progression studies and represents one of the most extensively investigated quantitative radiographic approaches. Baseline or longitudinal TBT characteristics predicted subsequent JSN or combined radiographic and symptomatic progression in several cohorts [11,23,26–28,31–34]. However, the incremental improvement over clinical and conventional radiographic predictors was not uniform, supporting the use of TBT/FSA as a complementary measure of subchondral bone architecture.

Artificial intelligence (AI), machine learning, and radiomics expanded the information extractable from conventional radiographs. Promising performance was reported for prediction of both incident and progressive outcomes, including external validation in some

studies [6,10,29,59]. Nevertheless, the available evidence does not establish that AI-derived features consistently outperform conventional or longitudinal quantitative radiographic measures across independent populations.

The current review was designed as an updated and more focused extension of the 2023 narrative review of radiographic KOA biomarkers [8]. Seventeen of the 24 unique studies included in the earlier review were retained in the current synthesis. Two studies were not retained because they represented longitudinal risk-factor or association analyses without assessment of predictive performance, while five evaluated total knee arthroplasty as a standalone prediction outcome, which was outside the scope of the current review. The updated evidence base additionally includes 21 studies that were not covered in the 2023 review, reflecting both the extended search period and the rapid development of AI, radiomics, longitudinal TBT analysis, and multimodal prediction. Whereas the earlier review considered radiographic biomarkers associated with KOA incidence, progression, and arthroplasty risk, the current review focuses specifically on longitudinal prediction of incident and progressive KOA, requires quantitative assessment of predictive performance, and organizes the evidence according to baseline disease stage and clinical prediction objective.

The current review also differs from the earlier TBT-focused review, which examined a broader range of trabecular-texture applications, including cross-sectional characterization, disease incidence and progression, treatment-related changes, and arthroplasty risk [60]. In the current synthesis, TBT/FSA is evaluated within a comparative framework encompassing conventional radiographic measures, quantitative morphology, radiomics, and artificial intelligence. This comparison allows its potential contribution to be considered alongside other radiographic biomarkers rather than as an isolated analytical approach.

4.2. Prediction of Incident Knee Osteoarthritis

Predicting incident KOA is particularly challenging because eligible knees generally have no definite radiographic disease at baseline, commonly corresponding to KL grades 0–1. The objective is therefore to identify subtle structural features associated with the future development of definite radiographic KOA before substantial joint-space loss has occurred.

The distinction between KL grade 0 and KL grade 1 appears prognostically relevant. Adding baseline KL grade to age, sex, and BMI substantially improved incident-KOA prediction [13]. Baseline KL grade 1 was also retained in an externally validated model for rapidly progressing incident tibiofemoral KOA [12]. Minor radiographic changes should therefore not be considered prognostically negligible, although their interpretation may remain affected by reader variability.

Quantitative joint morphology may refine early risk stratification. A two-stage random-forest model combining radiographic morphology with demographic predictors achieved better balanced accuracy than either morphology or demographic characteristics alone [9]. These findings suggest that alignment-related radiographic measures may be most useful as components of multifactorial models rather than as standalone predictors.

TBT/FSA offers a biologically plausible means of detecting early subchondral bone remodelling. In radiographically normal knees, baseline TBT improved prediction of incident KL-defined KOA, JSN, and osteophyte formation compared with models containing demographic variables alone [11]. The observation that baseline TBT features predict subsequent radiographic KOA is consistent with the hypothesis that detectable alterations in subchondral bone architecture may precede overt radiographic disease. However, further external validation using standardized acquisition and analysis protocols remains necessary.

Computational approaches have also identified radiographic information not readily appreciable through visual assessment. Computer-aided analysis of baseline KL grade 0 radiographs predicted subsequent development of radiographic KOA over approximately

20 years [14]. More recent machine learning models have combined radiographic reports, morphology, clinical factors, and demographic variables to predict incident disease [9,15]. Although encouraging, these findings do not demonstrate that computationally extracted features consistently replace or outperform simpler conventional predictors.

Collectively, the incidence studies support an integrative approach in KL grade 0–1 knees. Baseline KL grade remains informative, whereas morphology, alignment, TBT/FSA, and computational image analysis may provide additional information according to the population and prediction endpoint. The evidence supports complementarity rather than a fixed hierarchy in which advanced image analysis necessarily supersedes conventional radiographic assessment.

4.3. Prediction of Knee Osteoarthritis Progression

Once KOA is established, the prediction objective shifts from identifying disease susceptibility to estimating the subsequent trajectory of structural, symptomatic, or combined deterioration. Most progression studies included knees with baseline KL grades 1–3, although baseline severity and progression definitions differed substantially.

Conventional measures remained central to progression prediction. Baseline KL grade combined with pain severity predicted subsequent JSW loss and performed better than bone scintigraphy in women with established KOA [35]. In an externally validated machine learning model, baseline KL grade and medial and lateral JSN were among the most informative predictors of KL-grade progression [10]. These findings reinforce the value of conventional radiographic status for risk stratification in established disease.

Quantitative JSW measurements may offer additional sensitivity by detecting small longitudinal changes that are not captured by semiquantitative grading. Early changes in bilateral JSW were strongly predictive of longer-term structural trajectories [30].

TBT/FSA was repeatedly evaluated as a complementary predictor of structural progression. Baseline medial tibial FSA predicted medial JSN progression, with improved discrimination when combined with alignment, bone mineral content, and clinical covariates [34]. In a larger Osteoarthritis Initiative population, TBT and baseline JSN each contributed predictive information, while their combination with clinical variables further improved model performance [32]. Tibial TBT also predicted medial JSN progression in knees both with and without baseline radiographic KOA [23], and a related classifier-based approach demonstrated useful predictive performance [33].

The prognostic contribution of TBT was not restricted to purely structural outcomes. In the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium, baseline and longitudinal TBT composites modestly improved prediction of combined radiographic and pain progression compared with conventional covariates alone [31]. Subsequent analyses suggested that longitudinal TBT changes may provide more information than baseline texture alone [27,28]. Furthermore, models combining TBT-derived descriptors with convolutional neural networks demonstrated cross-cohort prediction of medial JSN progression in the Osteoarthritis Initiative and Multicenter Osteoarthritis Study [26].

Overall, TBT/FSA appears to capture aspects of subchondral bone architecture that are complementary to KL grade, JSN, and JSW. However, heterogeneity in radiographic acquisition, region-of-interest selection, image processing, texture algorithms, and progression definitions currently limits direct comparison between studies and argues against considering TBT/FSA a standalone replacement for established radiographic measures.

4.4. Artificial Intelligence and Radiomics

AI-based methods can learn complex image representations from conventional radiographs and combine these representations with clinical or conventional radiographic

predictors. Fusion of convolutional neural network–derived features with clinical variables achieved promising externally validated performance for predicting KOA progression, with further improvement after incorporation of baseline KL grade [29].

More recent studies have evaluated strategies intended to improve generalizability. Diagnostic pretraining improved external prediction of structural incidence and progression, whereas experience-replay methods helped preserve diagnostic performance during prognostic training [6]. An independently developed random-forest model incorporating readily available clinical and radiographic variables achieved an external-validation AUC of 0.76 in the Multicenter Osteoarthritis Study [10]. These findings demonstrate the feasibility of external validation but also indicate that performance can vary across cohorts and outcome definitions.

Radiomics provides a related approach based on predefined quantitative image features. Radiographic radiomics-based nomograms demonstrated promising performance for predicting pain progression, with reported calibration and decision-curve analyses [7]. However, this endpoint represented symptomatic rather than radiographic structural progression. The findings should therefore not be interpreted as direct evidence that radiomics predicts structural deterioration.

Importantly, the predictive performance of AI-based approaches cannot be directly compared with that of conventional radiographic measurements solely on the basis of AUC values reported across different studies. Variations in baseline disease severity, study populations, follow-up periods, prediction outcomes, predictor sets, and validation strategies may substantially influence model discrimination. Furthermore, the performance of AI models incorporating clinical, radiographic, or other imaging variables reflects the combined predictor set rather than the independent contribution of AI-derived features. Consequently, higher AUC values do not necessarily demonstrate the superiority of AI over conventional radiographic biomarkers. Such conclusions require head-to-head comparisons using the same populations, outcomes, prediction horizons, and validation procedures, ideally with assessment of the incremental predictive value of AI-derived features beyond established radiographic and clinical predictors.

AI and radiomics should currently be considered methods for integrating and extending information derived from conventional radiographs rather than distinct biological biomarkers or replacements for established measurements. Their implementation will require external validation, assessment of calibration and clinical net benefit, explainability, standardized image-processing procedures, and evaluation across radiographic equipment and clinical settings.

4.5. Standardization of Radiographic Acquisition and Quantitative Analysis

The reliability of quantitative radiographic biomarkers depends not only on the analytical method but also on the standardization of image acquisition. Variations in knee flexion, foot rotation, X-ray beam angle and centering, and medial tibial plateau alignment can alter the apparent joint-space width (JSW) and reduce the sensitivity of longitudinal measurements. In particular, inadequate reproducibility of medial tibial plateau alignment between serial radiographs has been shown to affect the detection of joint-space narrowing and its association with KOA progression [53]. Weight-bearing fixed-flexion or semiflexed posteroanterior projections should therefore be acquired using consistent positioning and beam geometry at each examination. Recent comparisons of radiographic JSW with three-dimensional JSW measured using weight-bearing computed tomography have also emphasized the importance of standardized acquisition when predicting subsequent structural or symptomatic worsening [36,37].

The radiographic projection should be selected according to the anatomical compartment and biomarker being evaluated. Posteroanterior weight-bearing fixed-flexion views are generally appropriate for tibiofemoral JSW, JSN, and subchondral tibial texture analyses. Conversely, lateral weight-bearing radiographs may provide complementary information on patellofemoral morphology. For example, quantitative analysis of patellar shape extracted from lateral radiographs was used to predict incident and end-stage KOA outcomes [17]. The selected projection, positioning device, knee-flexion angle, beam angle, source-to-image distance, and image-acquisition equipment should consequently be reported in sufficient detail to allow methodological reproduction.

Standardization is equally important during image processing. Studies evaluating trabecular bone texture (TBT) or fractal signature analysis (FSA) have used predefined regions of interest within the subchondral tibial bone; however, the location, dimensions, and placement procedures of these regions have differed among analytical pipelines [11,23,32,34]. These differences may influence the resulting texture descriptors and limit direct comparisons between studies. Regions of interest should therefore be defined using reproducible anatomical landmarks, and their compartment, dimensions, resolution, and placement method should be clearly reported. Automated ROI selection may reduce observer-dependent variability, but its repeatability should be evaluated across radiographic systems, disease stages, and image-quality levels [23,33].

Automated segmentation and computational feature extraction introduce additional standardization requirements. Deep learning segmentation can provide reproducible quantitative JSW measurements, but its performance depends on image resolution, pixel spacing, contrast, preprocessing, and the quality of the reference annotations [59]. Likewise, computer-aided analysis can identify prognostic image patterns that are not readily appreciable through visual assessment, although the features extracted may remain sensitive to acquisition and preprocessing differences [14]. Consequently, studies should describe image resizing, intensity normalization, segmentation, feature extraction, quality control, and exclusion of technically inadequate radiographs.

Data harmonization is particularly important when models are developed and validated across different cohorts or imaging centers. Differences in equipment, detector characteristics, pixel resolution, radiographic positioning, and post-processing may produce dataset-specific signals and reduce model transportability. Harmonization procedures should therefore address spatial resolution, intensity normalization, ROI placement, preprocessing, and feature calculation while preserving clinically meaningful biological variation. Any normalization or harmonization parameters should be estimated exclusively from the training data and subsequently applied unchanged to the validation dataset to prevent information leakage.

Before quantitative radiographic biomarkers can be implemented clinically, their repeatability, inter- and intra-reader reproducibility, robustness across acquisition systems, and external validity should be established. TBT/FSA has demonstrated predictive value across several longitudinal populations, including the OAI, MOST, and FNIH cohorts. This evidence encompasses baseline TBT/FSA measures, cross-cohort prediction, short-term TBT variations, and radiographic, symptomatic, and combined radio-symptomatic progression outcomes [26–28,31,43]. Nevertheless, differences in radiographic acquisition, ROI definition, and texture-processing methodology remain important barriers to direct comparison and clinical translation. Agreement on minimum standards for acquisition, positioning, ROI definition, image processing, quality control, and reporting would improve comparability between studies and facilitate the prospective multicenter validation of quantitative radiographic, radiomic, and AI-based prediction models.

4.6. Stage-Specific Interpretation and Clinical Implications

The distinction between incidence and progression provides the conceptual basis for the stage-specific framework proposed in Figure 2. In radiographically normal or near-normal knees, commonly KL grades 0–1, the objective is to identify structural susceptibility before definite KOA develops. Minor baseline KL abnormalities, quantitative morphology, alignment-related features, TBT/FSA, and computationally derived information may contribute to this objective [9,11–14,61].

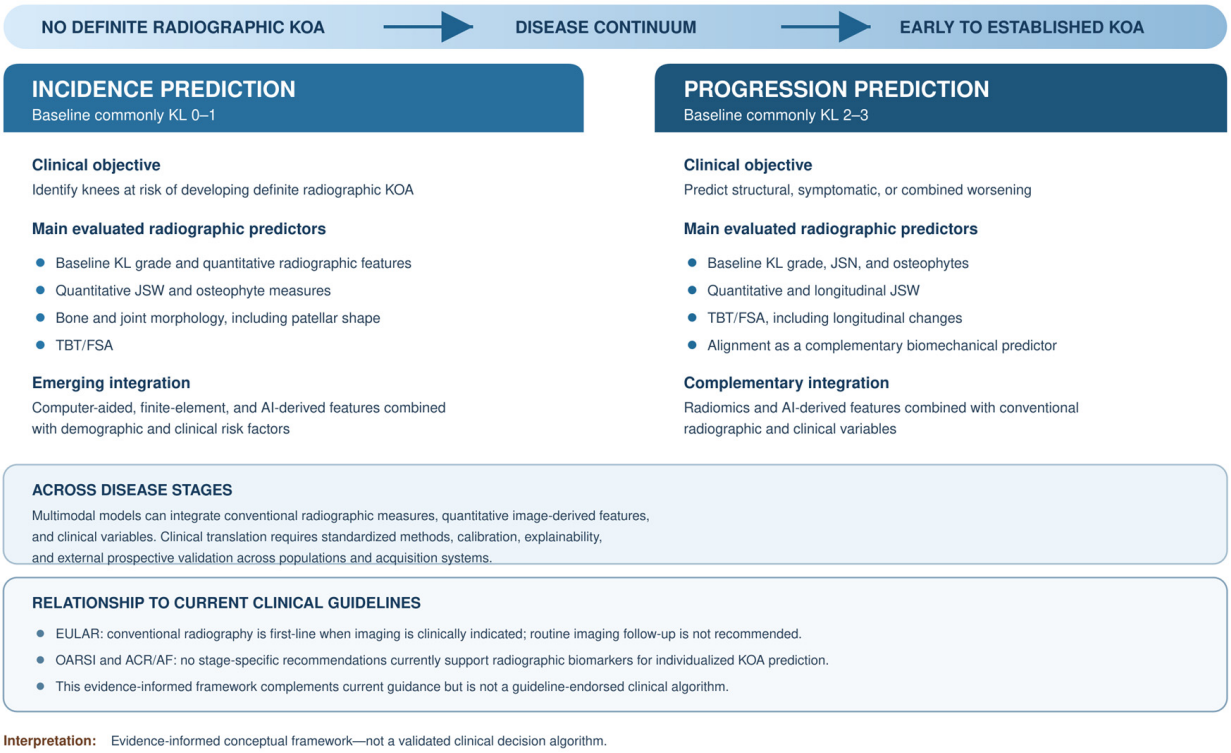

Figure 2. Stage-specific framework for selecting radiographic biomarkers for predicting incident and progressive knee osteoarthritis. Biomarker selection should be guided by both baseline Kellgren–Lawrence grade and the clinical prediction objective. Artificial intelligence is proposed for integrating information across disease stages. This framework represents an evidence-informed conceptual proposal based on heterogeneous studies. It has not been prospectively validated and is intended to guide future research rather than clinical decision-making. Abbreviations: KL, Kellgren–Lawrence grade; KOA, knee osteoarthritis; TBT/FSA, trabecular bone texture/fractal signature analysis; JSW, joint space width; JSN, joint space narrowing; AI, artificial intelligence; ACR/AF, American College of Rheumatology/Arthritis Foundation; EULAR, European Alliance of Associations for Rheumatology; OARSI, Osteoarthritis Research Society International.

For established radiographic KOA, particularly KL grades 2–3, the objective shifts toward identifying knees likely to experience structural or symptomatic deterioration. KL grade, JSN, JSW, early longitudinal JSW changes, and TBT/FSA provide relevant prognostic information [23,26,30–35].

AI may operate across both stages by integrating conventional radiographic, quantitative imaging, and clinical information [6,10,15,29,59]. It should therefore be considered an analytical strategy rather than a biomarker restricted to a particular disease stage.

The proposed stage-specific framework should be regarded as a conceptual, hypothesis-generating approach rather than a validated clinical decision tool. It was developed through qualitative synthesis of studies that differed in patient populations, radiographic assessment methods, prediction outcomes, follow-up periods, and analytical strategies. Consequently, the

proposed relationships between disease stage and biomarker selection have not been directly validated within a unified prediction framework. Prospective studies using standardized outcome definitions and head-to-head comparisons of biomarker combinations across baseline KL grades are required to assess its predictive performance, calibration, generalizability, and potential clinical utility before it can be considered for clinical implementation.

An important clinical implication is that conventional radiographs contain prognostic information beyond their traditional role in describing current structural severity. Quantitative analysis may increase the information obtainable from an imaging modality that is already inexpensive, standardized, and widely available. However, statistical prediction does not necessarily imply clinical utility. Before implementation, predictive models must demonstrate that their risk estimates meaningfully influence preventive interventions, monitoring strategies, treatment decisions, or recruitment into clinical trials.

In routine practice, conventional measures such as KL grade, JSN, and quantitative JSW are likely to remain the basis of radiographic staging and follow-up because they are familiar, interpretable, and widely available. If adequately validated, automated analysis of bone morphology, TBT/FSA, radiomics, and AI-derived features could add prognostic information to routinely acquired weight-bearing radiographs without requiring further imaging. In knees with KL grades 0–1, these approaches could help identify individuals who may benefit from closer monitoring or early preventive measures. In established KOA, they could help recognize patients at greater risk of structural or symptomatic worsening and inform follow-up, specialist referral, or selection for clinical trials. Their role should nevertheless remain complementary to clinical assessment rather than replacing clinical judgement.

Moving these biomarkers into routine care will require more than demonstrating good discrimination in a single cohort. Prospective multicenter studies should confirm their performance across different populations, radiographic systems, acquisition protocols, and clinical settings. Validation should also examine calibration, reproducibility, clinically meaningful risk thresholds, and whether the biomarkers provide useful information beyond established clinical and radiographic predictors. Consistent definitions of incidence and progression and comparable prediction horizons will be important for comparing results across studies. For AI-based approaches, transparent reporting, explainability, performance across patient subgroups, and evidence of practical benefit within the clinical workflow will also be needed before implementation.

4.7. Evidence Synthesis Across Radiographic Biomarkers

Across the included studies, substantial differences were observed in the predictive performance, level of validation, methodological standardization, and potential clinical applicability. Direct comparisons between biomarker categories were limited by heterogeneity in baseline disease severity, prediction horizon, outcome definition, analytical method, and validation strategy. Therefore, evidence maturity was evaluated qualitatively by considering the consistency of findings, availability of external validation, interpretability, and feasibility of implementation, rather than predictive performance alone. For multimodal studies, consideration was also given to whether the contribution of the radiographic component could be distinguished from that of the complete predictor set. Table 3 summarizes this evidence according to disease stage and biomarker category and reports the number of contributing studies, the number of distinct cohorts or data sources, the range of reported AUC or C-statistic values when available, and the corresponding supporting references.

Table 3. Evidence synthesis and clinical maturity of radiographic biomarkers for predicting knee osteoarthritis incidence and progression.

Prediction Objective	Biomarker Category	N° of Studies	Distinct Cohorts/Data Sources, n (Names)	Reported AUC/C-Statistics Range	Evidence Synthesis and Principal Limitations
Incidence	Conventional semiquantitative features	7 [10,13,15,16,20,22]	6 (Rotterdam Study I, Rotterdam Study II, Chingford, MOST, OAI, and PROOF)	0.66–0.81	Baseline KL grade, JSN, and other minor radiographic abnormalities contributed to incidence prediction, particularly when combined with clinical and contralateral-knee information. Reader dependence and limited sensitivity to subtle preradiographic changes remain important limitations.
Incidence	Quantitative JSW and osteophyte measures	2 [19,21]	2 (CHECK and PROOF)	0.64–0.74	Separate quantitative assessment of JSW, joint-space area, and osteophytes improved prediction beyond demographic or clinical variables. Evidence remains limited to relatively few cohorts and heterogeneous incidence outcomes.
Incidence	Morphology, shape, and computational biomechanics	4 [9,17,18,20]	2 (Chingford and OAI)	0.597–0.909	Knee morphology, patellar shape, and finite-element-derived features provided complementary structural or biomechanical information. Performance varied substantially according to the anatomical compartment and outcome, and independent external validation was limited.
Incidence	TBT/FSA	2 [11,23]	1 (OAI)	0.69–0.77	Baseline TBT/FSA predicted incident KL-defined KOA, JSN, and osteophyte development. Both studies used OAI data; therefore, validation in independent cohorts remains necessary.
Incidence	Computer-aided analysis, AI, and multimodal models	8 [9,10,14,15,17–19,22]	4 (OAI, MOST, PROOF, and BLSA)	0.597–0.909	Computational approaches extracted radiographic patterns or integrated radiographic information with demographic, clinical, or MRI variables. Some studies reported accuracy or balanced accuracy rather than AUC, and comparative external validation remains incomplete.
Progression	Conventional semiquantitative features	8 [10,15,22,24,25,35,41,42]	4 (OAI, MOST, Mazzuca clinical-trial cohort, and NYU clinical cohort)	0.66–0.95	KL grade, JSN, and osteophytes remained clinically interpretable predictors of structural or composite progression. The wide performance range reflects heterogeneity in predictor sets, endpoints, prediction horizons, and validation strategies.
Progression	Quantitative or longitudinal JSW	4 [30,36,37,42]	2 (OAI and MOST)	0.511–0.95	Baseline and early longitudinal JSW measurements contributed to structural-progression prediction. Performance was lower for symptomatic outcomes, and measurements remained sensitive to radiographic positioning, acquisition protocol, and the selected progression threshold.
Progression	Alignment and biomechanical features	1 [34]	1 (Prediction of Osteoarthritis Progression study)	0.75–0.79	Alignment provided complementary compartment-specific information when combined with FSA and clinical covariates. Its independent predictive contribution was not extensively evaluated.

Table 3. *Cont.*

Prediction Objective	Biomarker Category	N° of Studies	Distinct Cohorts/Data Sources, n (Names)	Reported AUC/C-Statistics Range	Evidence Synthesis and Principal Limitations
Progression	TBT/FSA	10 [23,26–28,31–34,40,43]	4 (OAI, MOST, Prediction of Osteoarthritis Progression study, and Pfizer A9001140 observational cohort)	0.608–0.85	TBT/FSA was evaluated across structural, symptomatic, and combined outcomes. Baseline and longitudinal texture changes provided complementary information, but acquisition, ROI placement, image processing, and analytical methods were heterogeneous. One classifier-based study reported accuracy rather than AUC.
Progression	Radiomics	1 [7]	1 (FNIH/OAI)	0.753–0.766	X-ray radiomics combined with clinical factors predicted sustained pain progression. The evidence is limited to one OAI-derived dataset and a symptomatic outcome.
Progression	AI and computational models	10 [6,10,15,24,26,29,38,39,42,44]	3 (OAI, MOST, and POMA)	0.70–0.95	AI models integrated raw radiographs, conventional radiographic features, and clinical information. External validation was performed in some studies, while others used internal hold-out samples. Some studies reported RMSE or AUC-PRC rather than conventional AUC.
Progression	Multimodal predictor sets	5 [22,38–41]	3 (OAI, NYU clinical cohort, and POMA)	0.641–0.832	Radiographs were combined with MRI, biochemical, or clinical variables. The independent or incremental contribution of the radiographic component could not always be isolated from that of the complete predictor set.

Study counts are not mutually exclusive because individual studies may evaluate more than one biomarker category or multimodal predictor set. Studies evaluating both incidence and progression were counted within each relevant prediction objective. Distinct cohorts or data sources were counted once within each row, irrespective of the number of publications derived from them. OAI-derived subsets, including the FNIH/OAI dataset, were considered part of OAI and were not counted as additional independent cohorts. Named clinical-trial and study-specific populations were retained as separate data sources. AUC and C-statistic ranges are reported only when available and may include models combining the indicated radiographic category with clinical or other imaging predictors. These ranges are descriptive and should not be interpreted as direct comparisons of biomarker superiority because populations, outcomes, prediction horizons, predictor sets, and validation strategies differed. AUC-PRC values were not combined with ROC-AUC or C-statistic ranges. Castagno et al. [58] reported AUC-PRC values of 0.724–0.806. Abbreviations: AI, artificial intelligence; AUC, area under the receiver operating characteristic curve; AUC-PRC, area under the precision–recall curve; BLSA, Baltimore Longitudinal Study of Aging; CHECK, Cohort Hip and Cohort Knee; FNIH, Foundation for the National Institutes of Health; FSA, fractal signature analysis; JSN, joint-space narrowing; JSW, joint-space width; KL, Kellgren–Lawrence; KOA, knee osteoarthritis; MOST, Multicenter Osteoarthritis Study; OAI, Osteoarthritis Initiative; PROOF, Prevention of Knee Osteoarthritis in Overweight Females; ROI, region of interest; TBT, trabecular bone texture.

Conventional radiographic biomarkers, including KL grade, JSN, osteophytes, and quantitative JSW, had the greatest clinical maturity. These features are widely available, readily interpretable, and already integrated into routine radiographic assessment. Baseline KL and JSN grades provided relevant predictive information for both incidence and progression, particularly when combined with clinical factors [10,12,13,15,16,20,24]. Separate quantitative assessment of osteophyte area and minimum JSW also improved incidence prediction [19,21], while quantitative and longitudinal JSW measurements demonstrated relevant information for structural-progression prediction [25,29,30,36,37]. Nevertheless, these measures often reflect structural abnormalities that are already visible on conventional radiographs, and their ability to predict symptomatic worsening was also less consistent [7,37].

Bone morphology and alignment provided complementary information on structural susceptibility and the biomechanical environment of the knee. Quantitative knee morphology improved incidence prediction when combined with demographic and conventional radiographic variables [9]. Patellar-shape analysis demonstrated compartment-specific predictive value [17], while X-ray-based finite-element simulation provided an additional method for predicting longer-term radiographic severity [18]. Alignment also contributed to models predicting compartment-specific progression [34]. However, the limited number of dedicated prediction studies and the heterogeneity of measurement methods currently restrict their independent clinical application.

TBT/FSA was the most extensively evaluated quantitative bone biomarker across the incidence and progression stages. Baseline TBT provided predictive information for incident KOA and subsequent JSN or osteophyte development [11,23]. TBT/FSA-based models predicted JSN, JSW loss, and radio-symptomatic progression [23,26,31–34,43], while longitudinal TBT changes further improved progression prediction beyond baseline clinical and radiographic variables [27,28]. TBT/FSA was also incorporated into multimodal imaging and biochemical models [40]. These findings support its complementary role in assessing subchondral bone architecture. Nevertheless, differences in radiographic acquisition, region-of-interest placement, image processing, and texture-analysis methodology remain barriers to standardization and widespread clinical implementation.

Radiomics and artificial intelligence enabled high-dimensional or deep learning features to be extracted directly from conventional radiographs and integrated with clinical and semiquantitative radiographic variables. Promising results were obtained for incident KOA, structural progression, symptomatic progression, and end-stage disease, with external validation performed in some cohorts [6,7,9,10,15,17,24,29,38,39,44]. Multimodal approaches additionally integrated radiographs with MRI, biochemical biomarkers, or other clinical variables [22,38–41]. However, the performance of these models reflects the complete predictor set, and the independent contribution of conventional radiography could not always be isolated. AI-derived features have therefore not demonstrated consistent superiority over conventional or longitudinal quantitative measures across independent populations.

Overall, conventional radiographic measures currently have the highest clinical readiness because of their accessibility, interpretability, and established use. TBT/FSA, morphology, alignment, radiomics, and AI may provide complementary predictive information, although the maturity and extent of validation differ considerably among these biomarker categories (Table 3). No advanced biomarker category has demonstrated consistent superiority over conventional or longitudinal quantitative radiographic measures across independent cohorts and standardized outcomes. The study and cohort counts and the reported performance ranges in Table 3 should therefore be interpreted as descriptive summaries rather than as direct comparisons of biomarker superiority.

4.8. Clinical Framework for Selecting Radiographic Biomarkers

Based on the evidence synthesized across the 38 included studies, an evidence-informed, stage-specific framework was developed to relate radiographic biomarker selection to baseline disease status and the intended prediction objective (Figure 2). The evidence supporting each component of the framework is summarized by disease stage and biomarker category in Table 3.

In knees without definite radiographic KOA, commonly KL grades 0–1, the clinical objective is to identify structural susceptibility before definite disease develops. Baseline KL grade, quantitative JSW and osteophyte measures, bone and joint morphology, patellar shape, alignment, and TBT/FSA may provide complementary information for predicting incident disease [9–23,36]. Conventional KL grading remains clinically interpretable

and widely available, whereas quantitative morphology, TBT/FSA, finite-element analysis, and AI-derived features may reveal additional structural or biomechanical susceptibility. However, the available evidence does not establish that advanced quantitative biomarkers consistently outperform appropriately constructed conventional radiographic–clinical models for incidence prediction.

In knees with early or established radiographic KOA, commonly KL grades 2–3, the prediction objective shifts toward identifying knees at risk of structural, symptomatic, or combined worsening. KL grade, JSN, osteophytes, quantitative JSW and longitudinal JSW changes remain the most clinically interpretable predictors of structural progression [10,24,25,30,35–37,42]. TBT/FSA may provide additional information on subchondral bone architecture across different disease stages [23,26–28,31–34,40,43]. Deep learning and radiomic models may additionally extract progression-related information from conventional radiographs or integrate radiographic features with clinical variables [6,7,26,29,38,39,44]. Because symptomatic and structural progression were not predicted equally well by the same biomarkers, biomarker selection should also be matched to the intended outcome domain.

AI and radiomics offer a means of integrating conventional and quantitative radiographic features with clinical variables, while multimodal models may additionally incorporate information from MRI, CT, or biochemical biomarkers [22,38–41]. However, the performance of such models should be attributed to the complete predictor set unless the independent or incremental contribution of conventional radiography has been specifically evaluated. Their generalizability and clinical utility require further external and prospective validation across populations, radiographic equipment, acquisition protocols, and healthcare settings. The proposed framework should also be considered in relation to current clinical guidance. EULAR recommends conventional radiography as the first-choice imaging modality when imaging is clinically indicated but does not recommend routine imaging during usual OA follow-up. Current OARSI and ACR/Arthritis Foundation recommendations primarily address clinical management and do not provide stage-specific guidance on using radiographic biomarkers for individualized prediction of KOA incidence or progression [62–64]. Accordingly, Figure 2 complements current guidance by synthesizing potential prognostic applications of conventional radiographs, but it should not be interpreted as a guideline-endorsed clinical algorithm.

More broadly, this stage-specific framework represents a conceptual synthesis derived from studies with heterogeneous populations, methodologies, prediction outcomes, and follow-up periods. It has not been prospectively validated and should therefore be regarded as a hypothesis-generating framework intended to guide future research rather than as a clinical decision tool for individual risk assessment or patient management.

4.9. Strengths and Limitations

A principal strength of this review is the explicit separation of incident KOA prediction from progression prediction. This distinction avoids assuming that biomarkers evaluated in established disease necessarily have the same prognostic value before definite radiographic OA develops. The review also integrates conventional measures, morphology, alignment, TBT/FSA, radiomics, and AI within a common clinical framework.

Several limitations should be acknowledged. First, this was a narrative review based primarily on PubMed/MEDLINE and restricted to English-language publications. Although a supplementary sensitivity search was conducted to improve coverage, relevant studies indexed exclusively in other databases, such as Embase, Scopus, or Web of Science, may have been missed, potentially limiting the comprehensiveness of the evidence synthesized. Furthermore, while a structured search and study-selection procedure was used, no formal

study-level risk-of-bias assessment using tools such as QUIPS or PROBAST was performed, and no quantitative meta-analysis was undertaken. Consequently, the qualitative assessment of evidence maturity presented in this review should not be interpreted as a formal rating of methodological quality or certainty of evidence.

Second, the included studies were heterogeneous regarding baseline KL grade, cohort composition, follow-up duration, radiographic acquisition, prediction horizon, predictor selection, outcome definition, and statistical methodology. Differences in model development and validation strategies further complicate the interpretation of reported AUC values. This heterogeneity precluded meaningful quantitative pooling and limits direct comparisons of predictive performance, particularly between AI-based approaches and conventional radiographic predictors evaluated in different populations or under different conditions. Furthermore, the proposed stage-specific framework was derived from this heterogeneous evidence base and has not been independently validated; its proposed biomarker–disease-stage relationships therefore remain exploratory.

Third, multiple publications used the same major longitudinal cohorts, particularly the Osteoarthritis Initiative, Multicenter Osteoarthritis Study, and Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. Apparently separate publications may therefore contain partially overlapping populations, and the number of included studies should not be interpreted as an equivalent number of independent validations.

Fourth, definitions of progression included KL-grade worsening, JSN progression, quantitative JSW loss, pain progression, combined radiographic and symptomatic progression, and knee replacement. Predictive performance must consequently be interpreted in relation to the specific endpoint and should not be compared directly across studies without considering these differences.

Finally, the evidence base for advanced approaches remains uneven. TBT/FSA has been evaluated in several longitudinal studies and across multiple outcomes, whereas prognostic radiomics remains represented by considerably fewer investigations. AI studies also differ substantially in model architecture, input variables, validation strategy, and reporting. These approaches should therefore remain exploratory until their reproducibility and incremental clinical value are established.

4.10. Future Perspectives

Future research should move beyond demonstrating associations toward establishing incremental and clinically useful prediction. New quantitative biomarkers should be compared directly with reference models incorporating baseline KL grade, JSN or JSW, age, BMI, symptoms, and other established predictors.

External validation is particularly important for AI and radiomics because model performance may be affected by population characteristics, disease prevalence, radiographic positioning, acquisition equipment, and image-processing pipelines. The external validation performed in several conventional and computational prediction studies demonstrates both the importance and feasibility of this approach [6,10,12,13,26,29].

Prospective studies should evaluate calibration, decision thresholds, clinical net benefit, explainability, and reproducibility rather than relying exclusively on AUC. Harmonization of radiographic acquisition, TBT/FSA processing, outcome definitions, and prediction horizons would facilitate comparison and replication. Analyses should also be stratified according to baseline disease stage to test the central hypothesis emerging from this review: the most informative combination of radiographic biomarkers may change as KOA evolves from structural susceptibility to established disease.

5. Conclusions

Conventional knee radiographs provide clinically relevant information for predicting incident and progressive KOA, although the most informative predictors vary according to baseline disease stage and the intended outcome. Minor KL abnormalities, quantitative JSW, osteophytes, and JSN contribute to incidence prediction, whereas KL grade, JSN, and quantitative JSW remain the principal interpretable measures for structural progression. TBT/FSA, quantitative morphology, radiomics, and AI-derived features may provide complementary predictive information, but no advanced biomarker has demonstrated consistent superiority across independent populations and standardized outcomes. The proposed stage-specific framework therefore remains conceptual rather than a validated clinical decision algorithm. Clinical translation requires harmonized acquisition protocols and outcome definitions, transparent reporting, and prospective multicenter external validation demonstrating reproducibility, calibration, incremental value, and clinical utility.

Author Contributions: Conceptualization, A.A.-I. and H.T.; methodology, A.A.-I. and H.T.; validation, A.A.-I., E.L. and H.T.; formal analysis, A.A.-I. and H.T.; writing—original draft preparation, A.A.-I. E.L. and H.T.; writing—review and editing, A.A.-I., H.T. and E.L.; supervision, H.T.; project administration, H.T.; funding acquisition, H.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the European Regional Development Fund (ERDF) and the City of Orléans, France, under funding reference EX004579. The authors gratefully acknowledge this financial support. Funding sources had no role in the study design, collection, analysis and interpretation of the data or the decision to submit the manuscript for publication.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Acknowledgments: OpenAI ChatGPT (GPT-5) was used during the preparation of this manuscript to assist with language editing, text refinement, readability improvement, and graphical design. All outputs generated by the tool were critically reviewed, revised, and verified by the authors, who take full responsibility for the final content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

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