SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-65016

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1–8, 2026

Original paper
Originalni naučni rad

A COMPOSITE SERUM INFLAMMATORY PHENOTYPE PREDICTS KNEE OSTEOARTHRITIS PROGRESSION

KOMPOZITNI SERUMSKI INFLAMATORNI FENOTIP U PREDVIĐANJU PROGRESIJE OSTEOARTRITISA KOLENA

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Summary

Background: To investigate the prognostic value of serum Interleukin-15 (IL-15), Tumour Necrosis Factor-alpha (TNF-α), and Chitinase-3-like protein 1 (YKL-40) for predicting structural and clinical progression in knee osteoarthritis (OA).
Methods: In a 36-month prospective cohort study, 320 participants with symptomatic knee OA (Kellgren-Lawrence [KL] grade 2–3) were assessed. Baseline serum biomarkers were quantified via high-sensitivity ELISA. The primary outcome was radiographic progression (increase in KL grade ≥1 or joint space narrowing [JSN] ≥0.5mm). Secondary outcomes included clinically important worsening in WOMAC pain (≥20%) and incidence of total knee arthroplasty (TKA).
Results: Elevated baseline levels of IL-15, TNF-α, and YKL-40 were independent predictors of radiographic progression after multivariate adjustment (IL-15: OR 2.41, 95% CI 1.52–3.81; TNF-α: OR 2.08, 1.31–3.30; YKL-40: OR 2.85, 1.81–4.49). A composite High-Risk Inflammatory Phenotype (HRIP), defined as elevation in ≥2 biomarkers, demonstrated superior predictive capacity (OR 5.12, 3.02–8.68 for radiographic progression; HR 3.45, 1.95–6.10 for TKA). The addition of the HRIP to a clinical model significantly improved predictive discrimination (AUC increase from 0.68 to 0.79, $p<0.001$).

Kratak sadržaj

Uvod: Cilj je bo da se ispita prognostička vrednost serumskog interleukina-15 (IL-15), faktora tumorske nekroze alfa (TNF-α) i proteina 1 sličnog hitinazi-3 (YKL-40) u predikciji strukturne i kliničke progresije osteoartritisa kolena (OA).
Metode: U prospektivnoj kohortnoj studiji u trajanju od 36 meseci je uključeno 320 ispitanika sa simptomatskim osteoartritisom kolena (Kellgren-Lawrence [KL] stadijum 2–3). Bazalni serumski biomarkeri su kvantifikovani pomoću visokoosetljivog ELISA testa. Primarni ishod bio je radiografska progresija (povećanje KL stadijuma ≥1 ili suženje zglobnog prostora [JSN] ≥0,5 mm). Sekundarni ishodi uključivali su klinički značajno pogoršanje bola prema WOMAC skoru (≥20%) i incidencu totalne artroplastike kolena (TKA).
Rezultati: Povišeni početni nivoi IL-15, TNF-α i YKL-40 su bili nezavisni prediktori radiografske progresije nakon multivarijantne analize (IL-15: OR 2,41; 95% CI 1,52–3,81; TNF-α: OR 2,08; 1,31–3,30; YKL-40: OR 2,85; 1,81–4,49). Kompozitni »High-Risk Inflammatory Phenotype« (HRIP), definisan povišenjem ≥2 biomarkera, pokazao je superiornu prediktivnu vrednost (OR 5,12; 3,02–8,68 za radiografsku progresiju; HR 3,45; 1,95–6,10 za TKA). Dodavanje HRIP modelu značajno je poboljšalo njegovu diskriminativnu moć (povećanje AUC sa 0,68 na 0,79;

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Conclusion: Serum IL-15, TNF-α, and YKL-40 define a novel systemic inflammatory signature. The HRIP panel is a robust, independent prognostic tool that identifies patients at high risk for rapid OA deterioration, with significant potential for clinical trial stratification and personalised management.

Keywords: osteoarthritis, biomarkers, prognosis, cytokines, IL-15, TNF-α, YKL-40, inflammation

p<0,001).
Zaključak: Serumski IL-15, TNF-α i YKL-40 definišu novi sistemski inflamatorni potpis. HRIP panel predstavlja snažan, nezavisan prognostički alat koji identifikuje pacijente sa visokim rizikom za brzu progresiju osteoartritisa, sa značajnim potencijalom za stratifikaciju u kliničkim studijama i personalizovani pristup lečenju.

Ključne reči: osteoartritis, biomarkeri, prognoza, citokini, IL-15, TNF-α, YKL-40, zapaljenje

Introduction

Osteoarthritis (OA) is a debilitating whole-joint disorder characterised by progressive cartilage degradation, synovial inflammation, and subchondral bone remodelling (1). Its clinical course is notoriously heterogeneous, with a significant subset of patients experiencing rapid structural and symptomatic decline (2, 3). This heterogeneity poses a major challenge for clinical management and drug development, underscoring the urgent need for prognostic biomarkers to identify »rapid progressors« at an early stage (4, 5).

The pathophysiology of OA extends beyond mere »wear and tear,« with low-grade, persistent inflammation – driven by a complex network of cytokines and chemokines – playing a central role in disease propagation (6, 7). While synovial fluid reflects the local joint environment, serum biomarkers offer a minimally invasive window into the systemic inflammatory milieu that may drive or reflect OA severity (8, 9). However, the prognostic utility of specific systemic cytokines remains controversial, and multibiomarker panels may offer superior predictive power than single analytes (10, 11).

This study focuses on three promising yet under-investigated serum biomarkers: Interleukin-15 (IL-15), Tumour Necrosis Factor-alpha (TNF-α), and Chitinase-3-like protein 1 (YKL-40). IL-15 is a potent pro-inflammatory cytokine that activates T-cells, natural killer cells, and macrophages, promoting a Th1-mediated immune response implicated in synovitis (12, 13). Cross-sectional data suggest its association with OA pain and severity, but prospective data are lacking (14). TNF-α, a master regulator of inflammation, is a validated therapeutic target in inflammatory arthritis. Its role in OA is more nuanced; while it drives cartilage catabolism in vitro, its prognostic value in serum is inconsistent, perhaps due to differences in paracrine vs systemic signalling (15, 16). YKL-40, secreted by activated chondrocytes and macrophages, is involved in tissue remodelling, angiogenesis, and protection against apoptosis. It has emerged as a promising marker of OA severity and progression, potentially reflecting active tissue turnover (17, 18).

We hypothesise that elevated baseline serum levels of IL-15, TNF-α, and YKL-40, individually and in combination, predict accelerated radiographic and clinical progression of knee OA over 36 months. This study aims to validate their prognostic utility and define a novel, clinically actionable high-risk inflammatory phenotype.

Materials and Methods

Study design and participants

This was a prospective, longitudinal study conducted from January 2023 to January 2026. We enrolled 320 participants aged 40–75 years with symptomatic primary knee OA, defined by American College of Rheumatology criteria and a baseline KL grade of 2 or 3 in the target knee (19). Key exclusion criteria included inflammatory arthritis (rheumatoid, psoriatic), recent intra-articular corticosteroid/hyaluronic acid injection (within 3 months), history of knee surgery or trauma, severe comorbid illness, or use of biologics/immunosuppressants. All participants provided written informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee. All participants provided written informed consent before enrolment. Data were anonymised before analysis to ensure participant confidentiality.

Biomarker measurement

Non-fasting venous blood was collected at baseline, processed within 2 hours, and serum aliquots were stored at -80 °C. Biomarkers were quantified in a single batch at the end of follow-up by investigators blinded to clinical data. IL-15 and TNF-α were measured using high-sensitivity Quantikine ELISA kits (R&D Systems, Minneapolis, MN), with lower detection limits of 0.1 pg/mL and 0.11 pg/mL, respectively. YKL-40 was measured using the MicroVue YKL-40 ELISA (Quidel, San Diego, CA). All inter- and intra-assay coefficients of variation were <10%. Values below the detection limit were assigned a value of half the lower limit.

Outcome assessments

- Radiographic Progression: Standardised fixed- flexion posterior-anterior knee radiographs were obtained at baseline and 36 months (20). Two experienced musculoskeletal radiologists, blinded to biomarker and clinical data, independently scored KL grades (0–4) and measured minimum joint space width (JSW) in millimetres using dedicated software (21). The primary outcome was radiographic progression, defined as either an increase in KL grade ≥1 or a reduction in JSW ≥0.5mm in the target knee (22).
- Clinical Progression: Patients completed the WOMAC pain subscale (0–20) at baseline and 36 months. Clinically important progression was defined as a worsening of ≥20% from baseline (23).
- Total Knee Arthroplasty (TKA): Incidence of TKA in the target knee during the follow-up period was recorded from medical records.

Inter-rater reliability was assessed using weighted Cohen's kappa (κ) for KL grading and intraclass correlation coefficients (ICC) for joint space width (JSW) measurements. Discrepancies in KL grading were resolved by consensus, and the mean of the two measurements was used for JSW analyses.

Covariates

Baseline data included age, sex, body mass index (BMI), baseline KL grade (2 vs 3), and baseline WOMAC pain score. Medication use during follow-up, including initiation of statins, metformin, and other agents with potential anti-inflammatory or metabolic effects, was recorded where available from medical records and patient self-report. Use of biologic therapies or disease-modifying anti-rheumatic drugs remained an exclusion criterion throughout the study period.

Statistical analysis

Biomarker concentrations were non-normally distributed and were log-transformed for analysis, and results were presented as median [interquartile range]. For categorical analysis, biomarkers were dichotomised as »High« or »Low« based on the optimal cut-off value for predicting radiographic progression determined by Youden's Index from Receiver Operating Characteristic (ROC) analysis. The composite »High-Risk Inflammatory Phenotype« (HRIP) was defined as having »High« levels in ≥2 of the three biomarkers.

Associations between biomarker categories and outcomes were analysed using multivariate logistic regression (for radiographic and WOMAC progression) and Cox proportional hazards regression (for TKA), adjusting for age, sex, BMI, baseline KL grade, and baseline pain. Results are presented as adjusted odds ratios (aOR) or hazard ratios (aHR) with 95% confidence intervals (CI). The incremental predictive value of adding biomarkers to a clinical model (age, sex, BMI, baseline KL grade) was assessed by comparing the area under the ROC curve (AUC) using the DeLong test (24). To assess the risk of model overfitting, the number of events per variable (EPV) was calculated for each multivariable model. An EPV≥10 was considered indicative of adequate model stability. Internal validation was performed using bootstrap resampling (1,000 iterations) to estimate model performance optimism. Optimism-corrected area under the receiver operating characteristic curve values were calculated for the primary models. Baseline KL grade was included as a covariate to account for underlying disease severity, given its established role as a strong predictor of osteoarthritis progression. To address potential bias arising from the inclusion of KL grade in both the covariate set and the outcome definition, sensitivity analyses were performed by excluding baseline KL grade and using continuous joint space width (JSW) change as an alternative outcome measure.

A sensitivity analysis was performed to evaluate the robustness of the primary findings and to address potential bias introduced by the adjustment for baseline KL grade. First, all multivariable models were repeated, excluding baseline KL grade from the covariate set. Second, an alternative analysis was conducted using continuous change in minimum joint space width (JSW, mm) over 36 months as the outcome, analysed using multivariable linear regression adjusted for age, sex, BMI, and baseline WOMAC pain. These analyses were designed to minimise potential collider bias and to confirm consistency of findings across outcome definitions. Statistical analyses were performed using Stata 18.0, with a two-sided p-value <0.05 considered significant.

Results

Cohort characteristics

Of the 320 enrolled participants, 298 (93.1%) completed the 36-month follow-up. The mean age was 62.4±8.1 years, 65% were female, and the mean BMI was 29.8±4.5 kg/m^2. Baseline characteristics of the overall cohort, stratified by progression status, are presented in *Table I*. Radiographic progression occurred in 124 participants (41.6%). Progressors had a higher baseline BMI than non-progressors (30.8 vs 29.1 kg/m^2), which, although

Table I Baseline characteristics of the study cohort.

Characteristic	Total Cohort (n=298)	Non-Progressors (n=174)	Progressors (n=124)	p-value
Demographics				
Age, years (mean ± SD)	62.4±8.1	61.8±8.3	63.2±7.8	0.145
Female, n (%)	194 (65.1)	108 (62.1)	86 (69.4)	0.195
BMI, kg/m^2 (mean ± SD)	29.8± 4.5	29.1±4.2	30.8±4.7	0.001
Clinical/Radiographic				
KL Grade 3, n (%)	142 (47.7)	68 (39.1)	74 (59.7)	<0.001
Baseline WOMAC Pain (0–20)	9.5 [7–12]	9 [6–11]	10 [8–13]	0.003
Serum Biomarkers				
IL-15, pg/mL	1.8 [1.2–2.7]	1.5 [1.0–2.2]	2.3 [1.7–3.4]	<0.001
TNF-a, pg/mL	2.1 [1.5–3.0]	1.9 [1.3–2.6]	2.5 [1.8–3.5]	<0.001
YKL-40, ng/mL	78.4 [52.1–112.5]	68.2 [45.3–98.7]	95.6 [68.4–135.2]	<0.001

Data presented as mean ± SD, n (%), or median [IQR]. BMI: Body Mass Index; KL: Kellgren-Lawrence; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table II Associations between baseline serum biomarkers and 36-month outcomes.

Biomarker Category	Radiographic Progression aOR (95% CI)*	p-value	WOMAC Pain Progression† aOR (95% CI)*	p-value	TKA Incidence aHR (95% CI)*	p-value
Individual (High vs. Low)						
IL-15 (>2.0 pg/mL)	2.41 (1.52–3.81)	<0.001	1.89 (1.20–2.98)	0.006	2.12 (1.14–3.94)	0.018
TNF-a (>2.3 pg/mL)	2.08 (1.31–3.30)	0.002	1.75 (1.11–2.76)	0.016	1.98 (1.06–3.71)	0.033
YKL-40 (>85 ng/mL)	2.85 (1.81–4.49)	<0.001	2.20 (1.40–3.46)	0.001	2.65 (1.43–4.91)	0.002
Combined Phenotype						
HRIP (≥2 High biomarkers)	5.12 (3.02–8.68)	<0.001	3.01 (1.79–5.07)	<0.001	3.45 (1.95–6.10)	<0.001

*aOR: adjusted Odds Ratio; aHR: adjusted Hazard Ratio. Adjusted for age, sex, BMI, baseline KL grade, and baseline WOMAC pain.
†WOMAC Pain progression defined as a ≥20% worsening from baseline*

modest in magnitude, was statistically significant. They also had a greater proportion of KL grade 3 disease and higher median serum levels of all three biomarkers.

During follow-up, 38 participants (12.8%) initiated statin therapy and 21 (7.0%) initiated metformin. No participants commenced disease-modifying anti-rheumatic drugs or biologic therapies. Adjustment for initiation of these medications in sensitivity analyses did not materially alter the associations between baseline biomarkers and outcomes.

*Individual and combine*d biomarker associations with prog*ression*

The optimal cut-offs for defining »High« biomarker levels were: IL-15>2.0 pg/mL, TNF-α>2.3 pg/mL, and YKL-40>85 ng/mL. In multivariate models, each »High« biomarker category was independently associated with radiographic progression (*Table II*). YKL-40 showed the strongest association (aOR 2.85). Participants with HRIP (≥2 high biomarkers) had a markedly elevated risk of all adverse outcomes compared with those with 0–1 high biomarkers (aOR 5.12 for radiographic progression; aOR 3.01 for WOMAC pain progression; aHR 3.45 for TKA).

Inter-rater reliability of radiographic assessments

Inter-rater agreement for KL grading between the two radiologists was excellent, with a weighted κ of 0.82 (95% CI 0.76–0.88). Agreement for JSW measurements was also excellent, with an intraclass correlation coefficient of 0.91 (95% CI 0.87–0.94).

Predictive performance of biomarker models

The clinical model (age, sex, BMI, KL grade) for predicting radiographic progression had an AUC of 0.68 (95% CI 0.62–0.74). Adding individual biomarkers improved the AUC modestly (IL-15: 0.72; TNF-α: 0.71; YKL-40: 0.75). The addition of the HRIP variable to the clinical model yielded the greatest improvement, increasing the AUC to 0.79 (95% CI 0.74–0.84), a statistically significant increase ($p<0.001$, DeLong test).

Sensitivity analyses

In sensitivity analyses excluding baseline KL grade from the multivariable models, the associations between serum biomarkers and radiographic progression remained materially unchanged. The HRIP phenotype continued to show a strong, independent association with progression (aOR 4.87, 95% CI 2.91–8.14), comparable to that in the primary model.

When radiographic progression was assessed using continuous JSW change, higher baseline levels of IL-15, TNF-α, and YKL-40 were each significantly associated with greater joint space loss over 36 months. The HRIP phenotype showed the strongest effect, with an adjusted mean JSW reduction of -0.42 mm ($p<0.001$) compared to participants without the phenotype.

Model stability and internal validation

For the primary outcome of radiographic progression, 124 events were observed. The multivariable models included six predictors, yielding an EPV of 20.7, exceeding recommended thresholds for reliable estimation.

Bootstrap validation demonstrated minimal optimism in model performance. The apparent AUC for the clinical model plus HRIP was 0.79, and the optimism-corrected AUC was 0.77, indicating limited overfitting. Similar findings were observed across models incorporating individual biomarkers.

Discussion

This prospective study provides evidence that a systemic inflammatory signature, defined by serum IL-15, TNF-α, and YKL-40, predicts structural and clinical deterioration in knee OA. Our key novel finding is that a composite High-Risk Inflammatory Phenotype (HRIP), defined by concurrent elevation of at least 2 of these biomarkers, identifies a patient subset with a 5-fold increased risk of radiographic progression and a 3.5-fold increased hazard of undergoing TKA within 3 years.

The independent prognostic value of each biomarker illuminates distinct pathogenic pathways. The association of IL-15 supports emerging evidence of adaptive immune system involvement in OA progression. IL-15 promotes the survival and activation of synovial CD8+ T cells and macrophages, driving a pro-catabolic environment (25, 26). Our prospective data extend prior cross-sectional work (27, 28), positioning IL-15 as a key mediator linking systemic immunity to joint damage. The role of TNF-α, though widely studied, has been ambiguous in serum (16, 29). Our findings confirm its relevance as a prognostic, if not purely diagnostic, systemic marker, potentially reflecting a more aggressive inflammatory synovitis phenotype (30, 31). The strongest individual association was with YKL-40, a glycoprotein implicated in tissue remodelling and chondrocyte stress response (18, 32). Its high levels likely indicate active extracellular matrix turnover and attempted repair, aligning with its correlation with rapid joint space loss (33, 34).

The synergistic predictive power of the HRIP panel is the most significant translational contribution. This aligns with the evolving paradigm of OA as a complex disorder with multiple inflammatory endotypes (35, 36). A single cytokine is unlikely to capture this complexity. The HRIP likely identifies patients with concurrent activation of immune-cell (IL-15), master inflammatory (TNF-α), and tissue-remodelling (YKL-40) pathways, representing a »perfect storm« for rapid progression (37). This panel significantly outperformed traditional clinical predictors, offering a practical tool for risk stratification.

Clinical implications

The HRIP panel could transform patient management and clinical trial design. It enables the identification of »rapid progressors« for inclusion in trials of disease-modifying OA drugs (DMOADs), enriching study cohorts and potentially reducing trial duration and cost (38, 39). Clinically, it could guide more frequent monitoring and justify earlier, more aggressive multimodal interventions (40).

Strengths & Limitations

Strengths include the prospective design, standardised outcome assessment, and analysis of a novel biomarker combination. This study has limitations, including: first, biomarker measurements were obtained at a single baseline time point, which limits the ability to assess the temporal dynamics of systemic inflammation. Serial measurements at intermediate intervals (e.g., 12 and 24 months) could provide additional prognostic insight by capturing trajectories of biomarker change or cumulative inflammatory burden over time (e.g., area-under-the-curve analyses). Such approaches may further refine risk stratification and should be explored in future studies (41–43).

Second, this was a single-centre study, which may limit generalisability. Although the cohort was well-characterised, external validation in independent populations is essential. In particular, validation across diverse ethnic groups, geographic regions, and healthcare systems is required to confirm the reproducibility and transportability of the High-Risk Inflammatory Phenotype (HRIP) before clinical implementation.

Conclusion

We define and validate a novel High-Risk Inflammatory Phenotype in knee OA based on serum IL-15, TNF-α, and YKL-40. This simple, blood-based composite panel is a powerful, independent prognostic tool that outperforms clinical factors alone. Its implementation could pave the way for a more personalised, prognostic approach to OA management and accelerate the development of targeted therapies.

Authors' contribution

Zungui Wu, Yu Liu, and Peigeng Xie contributed equally to this work and are regarded as co-first authors.

Funding

This work was supported by the Guangxi Natural Science Foundation (2021GXNSFBA220042) and the Science and Technology Plan Project of Qingxiu District, Nanning (2020034).

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

References

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019; 393(10182): 1745–59.
2. Dell'Isola A, Allan R, Smith SL, et al. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord 2016; 17: 425.
3. Karsdal MA, Michaelis M, Ladel C, et al. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthritis Cartilage 2016; 24(12): 2013–21.
4. Kraus VB, Blanco FJ, Englund M, et al. OARSI Clinical Trials Recommendations: Soluble biomarker assessments in clinical trials in osteo-arthritis. Osteoarthritis Cartilage 2015; 23(5): 686–97.
5. van Spil WE, Kubassova O, Boesen M, et al. Osteoarthritis phenotypes and novel therapeutic targets. Biochem Pharmacol 2019; 165: 41–8.
6. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016; 12(10): 580–92.
7. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013; 21(1): 16–21.
8. Mobasheri A, Rayman MP, Gualillo O, et al. The role of metabolism in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2017; 13(5): 302–11.
9. Saberi Hosnijeh F, Bierma-Zeinstra SMA, Bay-Jensen AC. Osteoarthritis year in review 2018: biomarkers (biochemical markers). Osteoarthritis Cartilage 2019; 27(3): 412–23.
10. van den Bosch MHJ, van Lent PLEM, van der Kraan PM. Identifying effector molecules, cells, and cytokines of innate immunity in OA. Osteoarthritis Cartilage 2020; 28(5): 532–43.
11. Bay-Jensen AC, Hoegh-Madsen S, Dam E, et al. Which elements are involved in reversible and irreversible cartilage degradation in osteoarthritis? Rheumatol Int 2010; 31(4): 435–42.
12. McInnes IB, Gracie JA. Interleukin-15: a new cytokine target for the treatment of inflammatory diseases. Curr Opin Pharmacol 2004; 4(4): 392–7.
13. Ruckert R, Brandt K, Ernst M, et al. Interleukin-15 stimulates macrophages to activate CD4+ T cells:

a role in the pathogenesis of rheumatoid arthritis? Immunology 2009; 126(1): 63–73.

14. Scanzello CR, Plaas A, Crow MK. Innate immune system activation in osteoarthritis: is osteoarthritis a chronic wound? Curr Opin Rheumatol 2008; 20(5): 565–72.
15. Wojdasiewicz P, Poniatowski ŁA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014; 2014: 561459.
16. Orita S, Koshi T, Mitsuka T, et al. Associations between proinflammatory cytokines in the synovial fluid and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee. BMC Musculoskelet Disord 2011; 12: 144.
17. Johansen JS, Jensen BV, Roslind A, et al. Serum YKL-40, a new prognostic biomarker in cancer patients and cancer patients with metastasis: a systematic review. Eur J Cancer 2006; 42(Suppl 1): 24.
18. Conrozier T, Carlier MC, Mathieu P, et al. Serum levels of YKL-40 and C reactive protein in patients with hip osteoarthritis and healthy subjects: a cross sectional study. Ann Rheum Dis 2004; 63(2): 149–52.
19. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986; 29(8): 1039–49.
20. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the radiographic protocol. Osteoarthritis Cartilage 2008; 16(12): 1433–41.
21. Duryea J, Li J, Peterfy CG, et al. Trainable rule-based algorithm for the measurement of joint space width in digital radiographic images of the knee. Med Phys 2000; 27(3): 580–91.
22. Ravaud P, Giraudeau B, Auleley GR, et al. Radiographic assessment of knee osteoarthritis: reproducibility and sensitivity to change. J Rheumatol 1996; 23(10): 1756–64.
23. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005; 64(1): 34–7.
24. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44(3): 837–45.
25. Alaaeddine N, Olee T, Hashimoto S, et al. Production of the chemokine RANTES by articular chondrocytes and role in cartilage degradation. Arthritis Rheum 2001; 44(7): 1633–43.
26. Quinn J, McInnes IB, Connolly M, et al. IL-15 promotes osteoclastogenesis via up-regulation of RANKL expression in fibroblast-like synoviocytes in rheumatoid arthritis. Arthritis Res Ther 2008; 10(Suppl 1): P37.
27. Scanzello CR, McKeon B, Swaim BH, et al. Synovial inflammation in patients undergoing arthroscopic meniscectomy: molecular cha-racterisation and relationship to symptoms. Osteoarthritis Cartilage 2011; 19(5): 599–605.
28. Daheshia M, Yao JQ. The interleukin 1beta pathway in the pathogenesis of osteoarthritis. J Rheumatol 2008; 35(12): 2306–12.
29. Livshits G, Zhai G, Hart DJ, et al. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford Study. Arthritis Rheum 2009; 60(7): 2037–45.
30. Stannus O, Jones G, Cicuttini F, et al. Circulating levels of IL-6 and TNF-a are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage 2010; 18(11): 1441–7.
31. Mabey T, Honsawek S, Tanavalee A, et al. Plasma and synovial fluid inflammatory cyto-kine profiles in primary knee osteoarthritis. Biomarkers 2016; 21(7): 639–44.
32. Volck B, Johansen JS, Stoltenberg M, et al. Studies on YKL-40 in knee joints of patients with rheumatoid arthritis and osteoarthritis. Involvement of YKL-40 in the joint pathology. Osteoarthritis Cartilage 2001; 9(3): 203–14.
33. Recklies AD, White C, Ling H. The chitinase 3-like protein human cartilage glycoprotein 39 (HC-gp39) stimulates proliferation of human connective tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signalling pathways. Biochem J 2002; 365(Pt 1): 119–26.
34. Gelse K, Söder S, Eger W, et al. Osteophyte development – molecular characterisation of differentiation stages. Osteoarthritis Cartilage 2003; 11(2): 141–148.
35. Deveza LA, Melo L, Yamato TP, et al. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthritis Cartilage 2017; 25(12): 1926–1941.
36. van der Esch M, Knoop J, van der Leeden M, et al. Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. Osteoarthritis Cartilage 2015; 23(4): 544–549.
37. Sohn DH, Sokolove J, Sharpe O, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. Arthritis Res Ther 2012; 14(1): R7.
38. Hunter DJ, Bowes MA, Eaton CB, et al. Can we identify patients with high risk of osteoarthritis progression who will respond to treatment? A focus on epidemiology and phenotype of osteoarthritis. Drugs Aging 2017; 34(12): 925–36.
39. Roemer FW, Hayes CW, Miller CG, et al. Imaging biomarkers for osteoarthritis. Radiology 2022; 305(3): 536–52.
40. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee,

hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019; 27(11): 1578–89.

41. Bay-Jensen AC, Reker D, Kjelgaard-Petersen CF, et al. Osteoarthritis year in review 2021: biomarkers (biochemical markers). Osteoarthritis Cartilage 2022; 30(2): 237–48.
42. Attur M, Krasnokutsky S, Statnikov A, et al. Low-grade inflammation in symptomatic knee osteoarthritis: prognostic value of inflammatory plasma lipids and peripheral blood leukocyte biomarkers. Arthritis Rheumatol 2015; 67(11): 2905–15.
43. Sanchez-Lopez E, Coras R, Torres A, et al. Synovial inflammation in osteoarthritis progression. Nat Rev Rheumatol 2022; 18(5): 258–75.

Received: April 12, 2026
Accepted: May 06, 2026