Journal of Advances in Medicine and Medical Research

Volume 36, Issue 11, Page 195-207, 2024; Article no.JAMMR.124397
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

A Comprehensive Review on Biomarkers for Osteoarthritis: Enhancing Diagnostic Accuracy and Prognostic Insights

Ngozi Amanze [a*], Oluwaseun Abayomi Oguntuase [b], Adetola Mowo-wale [c], Roshan Goswami [a], Luis Fernando Jimenez Cepeda [d], Ehimwenma Norense Osahon [e], Hafsa Aziz [f], Maryam Nour [g], Uzoamaka Amara Ogbu [h], Genesis Marie Muñoz [a], Eke Nwanne Okafor [i], Onyeka Chukwudalu Ekwebene [j], Vimla Devi [k], Frederick Ferguson [l] and Ayodele Paul Ogunro [a]

[a] American University of Antigua College of Medicine, Antigua & Barbuda.
[b] Caribbean Medical University, Curaçao.
[c] Obafemi Awolowo College of Health Sciences/Olabisi Onabanjo University, Nigeria.
[d] Universidad Libre Seccional Barranquilla (UL), Colombia.
[e] Kharkiv National University, Ukraine.
[f] Allama Iqbal Medical College, Pakistan.
[g] John F. Kennedy University School of Medicine, Curaçao.
[h] Enugu State University of Science and Technology College of Medicine, Nigeria.
[i] Sumy State University Medical Institute, Ukraine.
[j] Indiana University School of Medicine, USA.
[k] People's Medical College, Pakistan.
[l] Summa Health System, USA.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jammr/2024/v36i115630

**Corresponding author: E-mail: blessing915@gmail.com;*

Cite as: *Amanze, Ngozi, Oluwaseun Abayomi Oguntuase, Adetola Mowo-wale, Roshan Goswami, Luis Fernando Jimenez Cepeda, Ehimwenma Norense Osahon, Hafsa Aziz, Maryam Nour, Uzoamaka Amara Ogbu, Genesis Marie Muñoz, Eke Nwanne Okafor, Onyeka Chukwudalu Ekwebene, Vimla Devi, Frederick Ferguson, and Ayodele Paul Ogunro. 2024. "A Comprehensive Review on Biomarkers for Osteoarthritis: Enhancing Diagnostic Accuracy and Prognostic Insights". Journal of Advances in Medicine and Medical Research 36 (11):195-207. https://doi.org/10.9734/jammr/2024/v36i115630.*

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/124397

Systematic Review Article

Received: 08/08/2024
Accepted: 14/10/2024
Published: 31/10/2024

ABSTRACT

Objective: This systematic review aims to evaluate the current state of biomarkers in osteoarthritis (OA) management, focusing on their diagnostic, prognostic, and therapeutic utility. The review also assesses the potential of multi-marker models that integrate clinical and demographic data, and explores the relationships between OA and other systemic conditions.
Methods: A search of electronic databases comprising PubMed, Web of Science, Cochrane Library, and EMBASE was conducted, following the PRISMA guidelines, to identify relevant studies that discuss the role of biomarkers in OA. Special attention was given to studies evaluating the diagnostic accuracy, prognostic value, and therapeutic implications of these molecular indicators.
Results: Of the 736 studies identified, a total of 8 were included. Numerous biomarkers such as C-terminal telopeptide of collagen type II (u-CTX-II), serum cartilage oligomeric protein (COMP), N-terminal pro-B type natriuretic peptide (NT-proBNP), and high-sensitivity troponins T and I (hs-cTnT and hs-cTnI) have been explored for their potential role in cartilage degradation and disease progression in osteoarthritis (OA). These biomarkers, often associated with collagen and aggrecan metabolism in joint tissues, have been investigated for their diagnostic accuracy, prognostic value, and therapeutic implications. Despite these efforts, no individual biomarker has yet achieved the level of reliability and specificity required for individualized diagnosis or prognosis.
Conclusion: Biomarkers hold substantial promise in advancing our understanding and management of OA, but their individual application remains limited. A key limitation of this review is the small number of studies included, which may limit the generalizability of the findings. Integrated multi-marker models offer a more nuanced and effective risk assessment and could serve as a basis for individualized management strategies. The findings suggest that future research should focus on refining multi-marker models, exploring novel biomarkers, and elucidating the systemic implications of OA. Additionally, larger and more comprehensive studies are needed to validate these biomarkers' clinical utility.

Keywords: Osteoarthritis; biomarkers; diagnosis; prognosis; systemic diseases; multi-marker models.

1. INTRODUCTION

Osteoarthritis (OA) is an inflammatory condition affecting joints, marked by a slow but unrelenting disintegration of joint cartilage, the growth of bone spurs, increased density of subchondral bone, alterations in bone marrow, expansion of bone edges, inflammation of the synovial membrane, and tissue fibrosis [1]. OA does not just target the joint; it impacts the whole joint structure, including the surrounding muscles [2]. The condition has various root causes, intricate underlying mechanisms, and a complex array of molecular pathways that contribute to its pathology [3,4].

Current diagnostic methods fall short in identifying the initial changes in the cartilage indicative of OA [5,6]. While indicators like inflammation, pain, and unsteady movement are classic signs of the disease, biomarkers measurable in the synovial fluid, blood, and urine offer more precise diagnostic avenues for OA at different stages [7]. Numerous such biomarkers, signaling cartilage deterioration or the enzymes that trigger OA, have been discovered [8]. These biomarkers are increasingly used to pinpoint the disease's onset, gauge its severity, track its progression, provide prognostic information, and inform therapeutic choices.

Although magnetic resonance imaging (MRI) is an effective tool for capturing late-stage cartilage and bone damage in OA, it is not an early diagnostic tool [9]. In these circumstances, circulating biochemical markers and proxy

outcomes become increasingly crucial. They help detect the disease in its infancy and guide the selection of either a disease-modifying drug or alternative treatments to halt OA's advancement.

In recent years, biomarkers have gained prominence in the medical field for their potential role in predicting disease onset, assessing severity, and monitoring treatment efficacy. These biological indicators can be proteins, genes, or other molecules that offer insights into the physiological condition of an individual. In the context of osteoarthritis, biomarkers could provide valuable information on the underlying biochemical processes, possibly predicting the risk of developing OA or progressing to more severe stages of the disease.

Although a considerable body of research exists examining various potential biomarkers for OA, such as fasting plasma glucose, uCTX-II, and sVCAM-1, among others, findings are often inconsistent and inconclusive [10]. Moreover, many studies have primarily focused on one or a limited set of biomarkers, making it challenging to understand their predictive or diagnostic efficacy in a broader context. This systematic review aims to comprehensively evaluate the existing scientific literature on the potential of using biomarkers for risk assessment in osteoarthritis.

2. METHODS

2.1 Eligibility Criteria

- **Participants**: Studies involving patients diagnosed with OA or at risk of developing OA.
- **Intervention**: Studies that investigate the utility of biomarkers in assessing the risk, diagnosis, prognosis, or treatment of OA.
- **Study Design**: All study types, including Randomized Controlled Trials (RCTs), longitudinal cohort studies, observational cohort studies, and comparative cohort studies, were considered.
- **Outcome Measures**: Studies must report on the utility or potential utility of biomarkers in the risk assessment for OA, diagnosis, treatment tracking, or patient outcomes related to OA.

2.2 Information Sources

Adhering to the PRISMA Statement 2020 guidelines, a systematic electronic search was conducted across databases such as PubMed, Web of Science, Cochrane Library, and EMBASE. A manual search of related journals, conference proceedings, and reference lists of included studies was also conducted to ensure a comprehensive review. The final search concluded on 8th September 2023, without any language or time restrictions.

2.3 Search Strategy

We employed a comprehensive search strategy using keywords related to osteoarthritis and biomarkers. Keywords included "Osteoarthritis", "OA", "biomarkers", "risk assessment", "diagnosis", "prognosis", "treatment", "uCTX-II", "sVCAM-1", "YKL-40", "fasting plasma glucose", and other related terms. Both Medical Subject Headings (MeSH) and free-text terms were used to ensure a comprehensive search.

2.4 Study Selection

Two independent reviewers screened the titles and abstracts of studies identified through the search strategy for eligibility. Full-text articles were subsequently acquired and further assessed based on the defined eligibility criteria. Studies meeting all the criteria were included, while those not meeting these criteria were excluded.

2.5 Data Extraction and Synthesis

Data were extracted and summarized in a narrative synthesis focusing on the utility of biomarkers for risk assessment in OA. The extracted data were categorized and analyzed to understand their implications for clinical practice and future research needs. The synthesis was structured as follows: "author (year), title, study design, sample size, biomarkers examined, key outcomes, and comments." By adhering to this methodological framework, we aim to provide a comprehensive and balanced overview of the current state of research on the utility of biomarkers in the context of osteoarthritis risk assessment.

2.6 Methodological Quality Assessment

The quality of included studies was assessed using the Physiotherapy Evidence Database (PEDro) scale, which evaluates 11 key methodological criteria for randomized controlled trials (RCTs). The criteria include random allocation, concealed allocation, baseline comparability, blinding of participants, therapists, and assessors, adequacy of follow-up, intention-

to-treat analysis, and between-group comparisons for at least one key outcome. Cohort and observational studies were also assessed for baseline comparability, follow-up rates, and whether statistical comparisons were made for key outcomes.

Each included study was scored based on its compliance with the PEDro criteria, with a total possible score of 10 points for RCTs (excluding the eligibility criteria, which is not scored). Two independent reviewers assigned PEDro scores, and disagreements were resolved through consensus. The PEDro scoring results are summarized in Table 2, with higher scores indicating better methodological quality.

3. RESULTS

In the initial search, we identified 736 studies from various databases. After removing 43 duplicates, 693 studies remained for further examination. Screening based on titles and abstracts led to the exclusion of 637 studies due to irrelevance. An in-depth look was then given to 56 full-text articles, of which 48 were subsequently excluded for failing to meet our eligibility criteria. Finally, 8 studies were selected for inclusion in this systematic review. The progression of study selection is visually summarized in Fig. 1 through a PRISMA flowchart. The characteristics of the included studies are listed in Table 1.

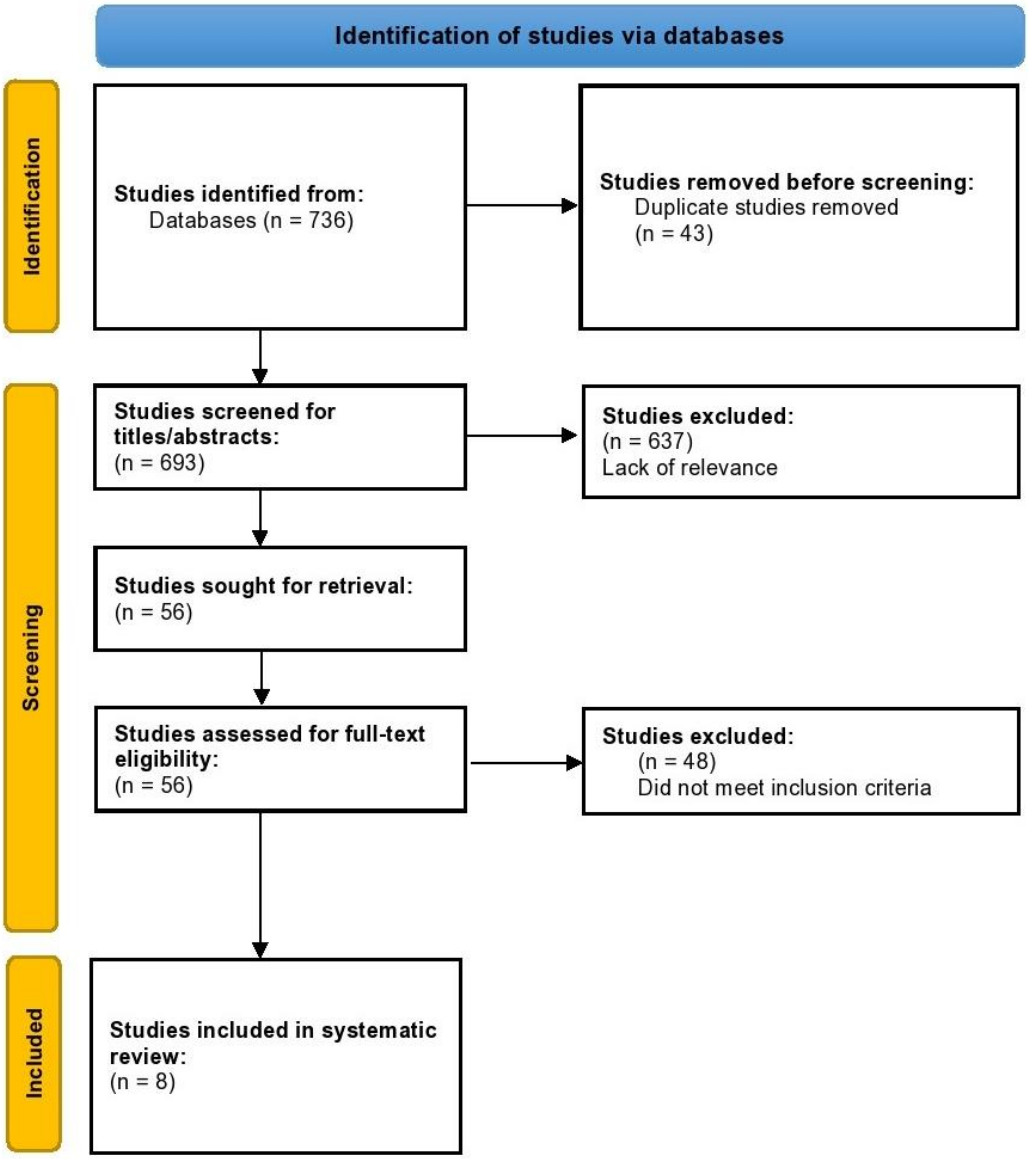

Fig. 1. PRISMA flowchart depicting the study selection process

Table 1. Characteristics of the included studies

Author, Year	Title	Study Design	Sample Size	Biomarkers Examined	Key Outcomes	Comments
Andersson et al., 2022 [11]	Cohort profile: the Halland osteoarthritis (HALLOA) cohort-from knee pain to osteoarthritis: a longitudinal observational study in Sweden	Longitudinal cohort study	306 individuals, mean age (SD) 51.7 (8.7) years, 69% are women	Fasting plasma glucose, visceral fat, total body fat	-Associations found between metabolic factors and radiographic knee OA, even in those with normal BMI -Clinical hand OA was positively associated with fasting plasma glucose. Increased visceral and total body fat were associated with increased pain sensitivity	The study indicates that metabolic factors and body composition, such as visceral fat and fasting plasma glucose, are associated with the early development of radiographic knee OA and increased pain sensitivity, providing potential avenues for risk prediction and therapeutic targeting
Bihlet et al., 2020 [12]	Clinical and biochemical factors associated with risk of total joint replacement and radiographic progression in osteoarthritis: Data from two phase III clinical trials	Cumulative data from two phase three clinical trials	1255 knee OA patients followed for two years	uCTX-II, along with baseline clinical variables like age, sex, and BMI	-A prediction model incorporating age, sex, BMI, CTX-II, and KL-grade predicted TJR within the two-year period with an AUC of 0.75 (95% CI: 0.72-0.77) -Participants with a cumulative KL-grade between knees of 5, 6, or 7 had a more than 3 times higher risk of TJR compared to lower (HR: 3.03, 95% CI: 1.54 to 5.96, P = 0.001) -Age was associated with increased TJR risk (per 5 years of age: HR: 1.28, 95% CI: 1.03-3.79, P = 0.05) -Baseline u-CTX-II was associated with elevated risk of radiographic progression	The study demonstrates that a composite model incorporating age, sex, BMI, and u-CTX-II can effectively predict total joint replacement and radiographic progression in knee OA patients over a two-year period
Haraden et al., 2019 [13]	Synovial fluid biomarkers associated with	Clinical Trial (Multivariable regression	48 knees from 25 participants	Soluble (s)VCAM-1, MMP-3, sICAM-1, TIMP-1, VEGF, MCP-	-Soluble (s)VCAM-1 and MMP-3 are significantly associated with synovial inflammation (FDR-	The study identifies six synovial fluid biomarkers linked to synovial

Author, Year	Title	Study Design	Sample Size	Biomarkers Examined	Key Outcomes	Comments
	osteoarthritis severity reflect macrophage and neutrophil related inflammation	with GEE and FDR correction)		1, CD163, CD14, elastase among 47 different cytokines, chemokines, and growth factors	adjusted P = 0.025 and 1.06 × 10^-7) -sVCAM-1, sICAM-1, TIMP-1, and VEGF are significantly associated with radiographic OA severity (P = 1.85 × 10^-5 to 3.97 × 10^-4) -VEGF, MMP-3, TIMP-1, sICAM-1, sVCAM-1, and MCP-1 are significantly associated with OA symptoms (P = 2.72 × 10^-5 to 0.050)	inflammation, radiographic severity, and symptoms in osteoarthritis, suggesting their utility in targeting therapies for individuals at high risk for knee OA progression
Karsdal et al., 2019 [14]	Serological biomarker profiles of rapidly progressive osteoarthritis in tanezumab-treated patients	Randomized Controlled Trial (Non-linear and linear multivariable predictive models using data from tanezumab trials)	47 cases (RPOA type-2) and 92 controls who used NSAIDs for either less than 90 days (limited users) or 90 days and above (chronic users)	Biochemical biomarkers of bone, cartilage, soft tissue, and synovial metabolism	-For limited NSAID users, the ROC curve area for RPOA type-2 was 71% [CI (60-83%)], and they had an 8-fold higher relative risk [CI (2-33)] -For chronic NSAID users, the AUC was 78% [CI (69-88%)], with a 4-fold relative risk [CI (2-6)] of developing RPOA type-2	The study identifies specific biomarker combinations that significantly increase the risk of developing RPOA type-2 in osteoarthritis patients who are either limited or chronic users of NSAIDs
Okada et al., 2019 [15]	Comparison of meniscal extrusion and osteophyte formation at the intercondylar notch as a predictive biomarker for incidence of knee osteoarthritis-Data from the Osteoarthritis Initiative	Comparative cohort study	2 cohorts (65 individuals in each cohort) were established from publicly available Osteoarthritis Initiative (OAI) data	Medial meniscal extrusion (ME) and osteophyte formation at the posterior condylar notch of the femur	-The AUC for ME evaluated by meniscus subluxation index (MSI) was 0.654 (95% CI: 0.561-0.748), and by medial radial displacement (MRD) was 0.677 (95% CI: 0.584-0.770) -The AUC for osteophyte formation, as assessed by WORMS score, was 0.667 (95% CI: 0.579-0.756)	The study demonstrates that both ME and osteophyte formation at the posterior condylar notch have similar predictive capacities for KOA development, suggesting potential for mass-screening
Kluzek et al., 2015 [16]	Serum cartilage oligomeric matrix protein and development of	Longitudinal cohort study	593 middle-aged women with no baseline KOA	Serum cartilage oligomeric matrix protein (sCOMP)	Highest quartile of sCOMP associated with increased risk of radiographic knee OA (RKOA) with an overall OR of 1.97 (95%	The study shows that elevated sCOMP levels serve as a predictive biomarker for the

Author, Year	Title	Study Design	Sample Size	Biomarkers Examined	Key Outcomes	Comments
	radiographic and painful knee osteoarthritis. A community-based cohort of middle-aged women				CI: 1.33-2.91) over 20 years compared to the lowest sCOMP quartile	development of structural and painful knee osteoarthritis over 20 years, independent of age and BMI
Kennish et al., 2014 [17]	Age-dependent ferritin elevations and HFE C282Y mutation as risk factors for symptomatic knee osteoarthritis in males: a longitudinal cohort study	2-year longitudinal observational study	127 patients with knee OA and 20 healthy controls	Serum ferritin, HFE gene mutation	-Higher levels of serum ferritin were found in patients older than 56 years (P=0.0186) and males (P=0.0006). HFE gene mutation more prevalent in OA patients -Higher ferritin in male patients was associated with narrower joint space width (P=0.032) and a nearly five-fold risk of radiographic severity (KL grade >2) (odds ratio = 4.74, P=0.023)	Serum ferritin levels are associated with symptomatic knee OA, particularly in older males, suggesting a potential role for iron stores in OA pathogenesis
Sanghi et al., 2013 [18]	Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial	Randomized Controlled Pilot Trial	107 patients with knee osteoarthritis and vitamin D insufficiency (25(OH)D ≤ 50 nmol/L)	Serum total calcium, 25(OH)D, and alkaline phosphatase	-Knee pain decreased in the vitamin D group by mean -0.26 on VAS and -0.55 on the WOMAC -Knee function improved in the vitamin D group by mean -1.36 over the placebo group -Significant biochemical changes in serum total calcium, 25(OH)D, and alkaline phosphatase	The study suggests that while vitamin D treatment led to clinical benefits in knee OA patients, the biochemical markers like serum total calcium, 25(OH)D, and alkaline phosphatase were altered but were not explicitly linked as risk predictors of OA progression

Abbreviations: *25(OH)D: 25-Hydroxyvitamin D; AUC: Area Under the Curve; BMI: Body Mass Index; CD14: Cluster of Differentiation 14; CD163: Cluster of Differentiation 163; CI: Confidence Interval; CTX-II: C-terminal telopeptide of type II collagen; FDR: False Discovery Rate; GEE: Generalized Estimating Equations; HALLOA: Halland Osteoarthritis; HFE: High Iron Fe (gene mutation); HR: Hazard Ratio; KL: Kellgren-Lawrence grade; KOA: Knee Osteoarthritis; MCP-1: Monocyte Chemoattractant Protein-1; ME: Medial Meniscal Extrusion; MMP-3: Matrix Metalloproteinase-3; MRD: Medial Radial Displacement; MSI: Meniscus Subluxation Index; NSAID: Non-Steroidal Anti-Inflammatory Drug; OA: Osteoarthritis; OAI: Osteoarthritis Initiative; OR: Odds Ratio; RPOA: Rapidly Progressive Osteoarthritis; sCOMP: Serum Cartilage Oligomeric Matrix Protein; SD: Standard Deviation; sICAM-1: Soluble Intercellular Adhesion Molecule-1; sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; TIMP-1: Tissue Inhibitor of Metalloproteinases-1; TJR: Total Joint Replacement; VAS: Visual Analogue Scale; VEGF: Vascular Endothelial Growth Factor; WOMAC: Western Ontario and McMaster Universities Arthritis Index; WORMS: Whole-Organ Magnetic Resonance Imaging Score*

Table 2. PEDro scoring table for included studies

Study (Author, Year)	Random Allocation	Concealed Allocation	Baseline Comparability	Blinding of Participants	Blinding of Therapists	Blinding of Assessors	Adequate Follow-up	Intention-to-Treat Analysis	Between-Group Comparisons	Measures of Variability	Total Score (out of 10)
Andersson et al., 2022 [11]	No	No	Yes	No	No	No	Yes	No	No	Yes	4/10
Bihlet et al., 2020 [12]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8/10
Haraden et al., 2019 [13]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Karsdal et al., 2019 [14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10
Okada et al., 2019 [15]	No	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Kluzek et al., 2015 [16]	No	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Kennish et al., 2014 [17]	No	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Sanghi et al., 2013 [18]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8/10

Andersson et al. conducted a longitudinal cohort study with 306 participants in Sweden, primarily women, with an average age of 51.7 years [11]. The study aimed to understand the relationship between metabolic factors and OA. They specifically examined fasting plasma glucose, visceral fat, and total body fat. Notably, they found associations between these metabolic factors and the early development of radiographic knee OA. This is particularly groundbreaking because it was observed even in individuals with a normal Body Mass Index (BMI). The study suggests that we should consider metabolic factors as important variables for risk prediction and potential therapeutic targeting in OA.

Bihlet and colleagues integrated data from two phase III clinical trials, involving 1255 knee OA patients over a two-year period [12]. Their study developed a composite model that incorporates age, sex, BMI, and a specific biomarker, u-CTX-II, to predict the risk of total joint replacement and radiographic progression in knee OA patients. The model yielded an AUC of 0.75, indicating good predictive power, which is particularly useful for clinicians in making evidence-based decisions regarding treatment and surgery.

This clinical trial led by Haraden et al. studied 48 knees from 25 participants to identify biomarkers associated with OA severity [13]. The biomarkers studied included sVCAM-1, MMP-3, and others. The findings highlight the role of these markers in synovial inflammation, radiographic OA severity, and symptoms. These biomarkers could be useful in identifying individuals at a high risk of knee OA progression, thereby aiding in targeted therapeutic interventions.

The randomized controlled trial by Karsdal et al. focused on the risk of developing rapidly progressive osteoarthritis (RPOA type-2) in patients using NSAIDs either limitedly or chronically [14]. This study is critical because it identified particular combinations of biochemical markers that were significantly associated with an increased risk of developing RPOA type-2, providing a new perspective on the effects of NSAID usage in OA patients.

Okada and team performed a comparative cohort study with 130 individuals to assess medial meniscal extrusion (ME) and osteophyte formation as predictive biomarkers for knee OA [15]. They found that both markers have similar capacities for predicting the development of knee OA, thereby suggesting their suitability for large-scale screenings to identify at-risk populations.

Kluzek's longitudinal cohort study followed 593 middle-aged women without baseline knee OA. The study found that elevated levels of serum cartilage oligomeric matrix protein (sCOMP) were associated with an increased risk of developing structural and painful knee OA over a 20-year period, independent of age and BMI [16]. This long-term view is particularly valuable for understanding OA progression in women.

Kennish and colleagues presented a two-year longitudinal observational study with 127 knee OA patients and 20 healthy controls [17]. They discovered that higher levels of serum ferritin, particularly in males older than 56, were associated with symptomatic knee OA. This suggests that iron stores could play a role in OA pathogenesis, offering a new avenue for investigation and potentially, intervention.

Sanghi et al. performed a randomized controlled pilot trial with 107 knee OA patients who also had vitamin D insufficiency [18]. The study found that vitamin D supplementation led to clinical benefits, including reduced knee pain and improved function. However, it was inconclusive in linking changes in biochemical markers like serum total calcium and 25(OH)D to OA progression, indicating a need for further research in this area.

To assess the methodological quality of the included studies, the PEDro scale was utilized. The studies varied in quality, with scores ranging from 4/10 to 10/10. The randomized controlled trials (RCTs) such as Karsdal et al. [14] and Bihlet et al. [12] achieved the highest methodological rigor, fulfilling most of the PEDro criteria including randomization, allocation concealment, and blinding. These studies provided strong evidence for the utility of biomarkers in OA management (Table 2).

In contrast, cohort studies such as Andersson et al. [11] and Okada et al. [15] lacked randomization and blinding, resulting in moderate scores. While these studies contributed valuable insights into OA biomarkers, the lack of rigorous methodological design limits the strength of their conclusions compared to the higher-quality RCTs.

4. DISCUSSION

This systematic review synthesized data from 8 studies to explore the utility of biomarkers in risk

assessment for osteoarthritis OA. Our results support the growing body of evidence that various biochemical markers measurable in serum, urine, and synovial fluid can play a significant role in identifying early stages of OA, gauging its severity, and even predicting its progression. Markers such as fasting plasma glucose, uCTX-II, and sVCAM-1 emerged as particularly promising.

Numerous biomarkers are being studied to understand joint remodeling and the progression of OA. These biomarkers range from those linked to collagen metabolism in either cartilage or bone to those related to non-collagenous proteins and inflammatory pathways [19]. Despite their utility, these markers have not yet proven fully effective for diagnosis or prognosis on an individual level. This shortcoming pinpoints the need for a more robust set of biomarkers that could act as reliable surrogate outcomes in clinical trials or predictive tools for disease onset and progression.

Notably, recent studies have examined biomarkers that also forecast comorbidities and mortality risks associated with OA [20–22]. For instance, elevated levels of growth differentiation factor-15 (GDF-15) have been highlighted as a significant predictor of all-cause mortality in OA patients [23]. Such findings encourage the inclusion of markers that predict other health risks, thereby contributing to a more holistic disease management strategy.

Although biomarkers like NT-proBNP and high-sensitivity troponins T and I have been associated with increased mortality, they are not fully conclusive due to confounding variables like age, sex, and cardiovascular factors [24]. This indicates a need for more nuanced models that take into account multiple variables to provide a comprehensive risk profile.

Emerging evidence suggests an intricate relationship between metabolic conditions like diabetes mellitus and OA. While initial results have indicated that markers of abnormal glucose metabolism might be linked to OA, these findings lose statistical significance when accounting for body mass index (BMI), necessitating further study to tease out these associations.

Our findings align with prior research emphasizing the importance of biomarkers in OA diagnosis and management [25–27]. However, unlike previous studies that often focus on single markers, our review takes a holistic approach, considering a variety of markers and their implications across different stages of the disease. For instance, our review corroborates the work of Andersson et al., which found metabolic factors to be critical in early OA development. Likewise, our analysis complements the study by Bihlet et al., which demonstrated the efficacy of composite models incorporating biomarkers and clinical variables in predicting total joint replacement.

Multi-marker models hold significant promise for practical application in clinical settings. By incorporating multiple biomarkers alongside demographic and clinical factors such as age, sex, and BMI, these models could offer a more comprehensive risk profile for patients at various stages of OA. For instance, such models could be integrated into electronic health records (EHRs) to provide real-time, evidence-based recommendations for early intervention or modification of existing treatments. Additionally, the development of point-of-care testing technologies that enable the rapid quantification of biomarker panels could further enhance their utility in routine clinical practice, enabling more personalized and timely management strategies.

Despite the wealth of research on OA biomarkers, the reliability and specificity of individual biomarkers remain a challenge. Biomarkers such as u-CTX-II and sCOMP have shown promise in identifying cartilage degradation and disease progression; however, their performance across different patient populations has been inconsistent. Variability in the sensitivity of these markers to confounding variables like age, BMI, and comorbidities has limited their standalone diagnostic and prognostic utility. To overcome these limitations, combining multiple biomarkers in composite models improves the accuracy and specificity of risk assessments. These models not only mitigate the weaknesses of single biomarkers but also provide a more holistic understanding of OA's multifactorial nature, which is crucial for individualized patient care.

One of the strengths of this review is its comprehensive search strategy, aimed at capturing a broad spectrum of relevant studies. Furthermore, the use of the PRISMA guidelines ensures a rigorous methodology. However, our review is not without limitations. The heterogeneity in study designs and sample sizes among the included studies could affect the robustness of our conclusions. Additionally, not

all studies provided long-term follow-up data, limiting our ability to comment on the long-term predictive power of these biomarkers. Our study highlights the need for further research to validate the identified biomarkers through large-scale, multi-center trials [28–32]. For clinical practice, our findings suggest that a multi-marker approach could offer a more nuanced and comprehensive overview of OA status, aiding in more accurate diagnosis and targeted therapeutic interventions.

5. CONCLUSION

In sum, the potential for biomarkers to revolutionize our comprehension and therapeutic approaches for OA is required. These molecular indicators serve as windows into the physiological processes underlying joint deterioration and could substantially facilitate early diagnosis and targeted interventions. However, the existing pool of biomarkers has yet to reach the level of reliability and specificity required for individualized diagnostic and prognostic applications. As it stands, no single biomarker can fully discriminate between patients and healthy controls, or categorize patients according to varying degrees of disease severity. The advent of multi-marker models is a noteworthy advancement in this context. By integrating a range of biomarkers with demographic and clinical variables, such as age, sex, and BMI, these models offer a more nuanced and comprehensive risk assessment for OA. Such complex algorithms have the potential to improve predictive accuracy, thus enabling clinicians to tailor management strategies more effectively based on individual patient profiles.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Reinus WR. Systematic approach to arthropathies. Diagnostic Imaging Musculoskelet Dis A Syst Approach. 2010;407–96.
2. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A disease of the joint as an organ. Arthritis Rheum. 2012;64(6):1697.
3. Chen DI, Shen J, Zhao W, Wang T, Han L, Hamilton JL, et al. Osteoarthritis: Toward a comprehensive understanding of pathological mechanism. Bone Res. 2017;5(1):1–13.
4. Ni Z, Zhou S, Li S, Kuang L, Chen H, Luo X, et al. Exosomes: Roles and therapeutic potential in osteoarthritis. Bone Res. 2020;8(1):25.
5. Kraus VB, Burnett B, Coindreau J, Cottrell S, Eyre D, Gendreau M, et al. Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis. Osteoarthr Cartil. 2011;19(5):515–42.
6. Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, et al. Classification of osteoarthritis biomarkers: A proposed approach. Osteoarthr Cartil. 2006;14(8):723–7.
7. Kumavat R, Kumar V, Malhotra R, Pandit H, Jones E, Ponchel F, et al. Biomarkers of joint damage in osteoarthritis: Current status and future directions. Mediators Inflamm. 2021;2021.
8. McAllister MJ, Chemaly M, Eakin AJ, Gibson DS, McGilligan VE. NLRP3 as a potentially novel biomarker for the management of osteoarthritis. Osteoarthr Cartil. 2018;26(5):612–9.
9. Hunter DJ, Arden N, Conaghan PG, Eckstein F, Gold G, Grainger A, et al. Definition of osteoarthritis on MRI: Results of a Delphi exercise. Osteoarthr Cartil. 2011;19(8):963–9.
10. Bernotiene E, Bagdonas E, Kirdaite G, Bernotas P, Kalvaityte U, Uzieliene I, et al. Emerging technologies and platforms for the immunodetection of multiple biochemical markers in osteoarthritis research and therapy. Front Med. 2020;7:572977.

11. Andersson MLE, Haglund E, Aili K, Bremander A, Bergman S. Cohort profile: The Halland osteoarthritis (HALLOA) cohort–from knee pain to osteoarthritis: A longitudinal observational study in Sweden. BMJ Open. 2022;12(7):e057086.
12. Bihlet AR, Bjerre-Bastos JJ, Andersen JR, Byrjalsen I, Karsdal MA, Bay-Jensen A-C. Clinical and biochemical factors associated with risk of total joint replacement and radiographic progression in osteoarthritis: Data from two phase III clinical trials. In: Seminars in Arthritis and Rheumatism. Elsevier. 2020;1374–81.
13. Haraden CA, Huebner JL, Hsueh M-F, Li Y-J, Kraus VB. Synovial fluid biomarkers associated with osteoarthritis severity reflect macrophage and neutrophil related inflammation. Arthritis Res Ther. 2019;21(1):1–9.
14. Karsdal MA, Verburg KM, West CR, Bay-Jensen AC, Keller DS, Arends R. Serological biomarker profiles of rapidly progressive osteoarthritis in tanezumab-treated patients. Osteoarthr Cartil. 2019;27(3):484–92.
15. Okada K, Yamaguchi S, Sato Y, Enomoto T, Ogawa Y, Ohtori S, et al. Comparison of meniscal extrusion and osteophyte formation at the intercondylar notch as a predictive biomarker for incidence of knee osteoarthritis-Data from the Osteoarthritis Initiative. J Orthop Sci. 2019;24(1):121–7.
16. Kluzek S, Bay-Jensen A-C, Judge A, Karsdal MA, Shorthose M, Spector T, et al. Serum cartilage oligomeric matrix protein and development of radiographic and painful knee osteoarthritis. A community-based cohort of middle-aged women. Biomarkers. 2015;20(8):557–64.
17. Kennish L, Attur M, Oh C, Krasnokutsky S, Samuels J, Greenberg JD, et al. Age-dependent ferritin elevations and HFE C282Y mutation as risk factors for symptomatic knee osteoarthritis in males: A longitudinal cohort study. BMC Musculoskelet Disord. 2014;15(1):1–9.
18. Sanghi D, Mishra A, Sharma AC, Singh A, Natu SM, Agarwal S, et al. Does vitamin D improve osteoarthritis of the knee: A randomized controlled pilot trial. Clin Orthop Relat Res. 2013;471: 3556–62.
19. Lotz M, Martel-Pelletier J, Christiansen C, Brandi ML, Bruyère O, Chapurlat R, et al. Republished: Value of biomarkers in osteoarthritis: Current status and perspectives. Postgrad Med J. 2014;90(1061):171–8.
20. Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in osteoarthritis: A systematic review and meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2020;72(7):991–1000.
21. Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis. Curr Opin Rheumatol. 2017;29(2):214–22.
22. Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO. Association between osteoarthritis and cardiovascular disease: Systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23(9):938–46.
23. Arnold N, Rehm M, Büchele G, Peter RS, Brenner RE, Günther K-P, et al. Growth differentiation Factor-15 as a potent predictor of long-term mortality among subjects with osteoarthritis. J Clin Med. 2020;9(10):3107.
24. Rehm M, Büchele G, Peter RS, Brenner RE, Günther K-P, Brenner H, et al. Relationship between cardiac biomarker concentrations and long-term mortality in subjects with osteoarthritis. PLoS One. 2020;15(12):e0242814.
25. Kraus VB. Do biochemical markers have a role in osteoarthritis diagnosis and treatment? Best Pract Res Clin Rheumatol. 2006;20(1):69–80.
26. Weber AE, Bolia IK, Trasolini NA. Biological strategies for osteoarthritis: from early diagnosis to treatment. Int Orthop. 2021;45:335–44.
27. Braaten JA, Banovetz MT, DePhillipo NN, Familiari F, Russo R, Kennedy NI, et al. Biomarkers for osteoarthritis diseases. Life. 2022;12(11):1799.
28. Carlson AK, Rawle RA, Adams E, Greenwood MC, Bothner B, June RK. Application of global metabolomic profiling of synovial fluid for osteoarthritis biomarkers. Biochem Biophys Res Commun. 2018;499(2): 182–8.
29. J Hunter D, Losina E, Guermazi A, Burstein D, N Lassere M, Kraus V. A pathway and approach to biomarker validation and qualification for osteoarthritis clinical trials. Curr Drug Targets. 2010;11(5):536–45.
30. Mobasheri A, Bay-Jensen A-C, Van Spil WE, Larkin J, Levesque MC. Osteoarthritis Year in Review 2016:

Biomarkers (biochemical markers). Osteoarthr Cartil. 2017;25(2): 199–208.

31. Hunter DJ, Nevitt M, Losina E, Kraus V. Biomarkers for osteoarthritis: Current position and steps towards further validation. Best Pract Res Clin Rheumatol. 2014;28(1):61–71.
32. Wang Y, et al. Machine learning-based biomarker discovery for osteoarthritis diagnosis: A systematic review. Osteoarthr Cartil. 2023;31(1):15-25.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/124397