

Synovial Fluid Biomarkers: Current Applications and Future Perspectives

Vassilia Terzieva^{1*}, Georgi Kotov^{1,2}, Mariana Ivanova^{1,3}

1. Clinic of Rheumatology, University Hospital "St. Ivan Rilski", Sofia, Bulgaria

2. Department of Rheumatology, Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria

3. Department of Internal Medicine, Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria

* Correspondence:

Vassilia Terzieva

Clinic of Rheumatology, University Hospital "St. Ivan Rilski"
Sofia, Bulgaria

Email: drterzievavassilia@gmail.com

ORCID: 0009-0002-3070-5979

Running title: Synovial Fluid Biomarkers: Overview

Abstract

Synovial fluid offers a direct window into the intra-articular environment, but individual biomarkers rarely separate arthritis subtypes reliably. This narrative review compares conventional tests with cytokines, proteomic markers, extracellular vesicles, microRNAs, metabolomics, and machine-learning-assisted multi-omics across rheumatoid arthritis, osteoarthritis, psoriatic arthritis, septic arthritis, periprosthetic joint infection, crystal-induced arthritis, connective tissue disease-associated arthritis, and Lyme arthritis. Relevant publications from 2017–2026 were identified through structured searches of PubMed, Scopus, Web of Science, and Google Scholar, supplemented by manual screening of reference lists; selection prioritized systematic and narrative reviews, translational studies, and clinically relevant biomarker investigations, and reporting followed the SANRA framework for narrative reviews.

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The most clinically mature applications remain conventional cell count, crystal analysis, microbiological testing, and alpha-defensin assessment for periprosthetic joint infection, whereas extracellular vesicles, microRNAs, and multi-omics remain largely translational.

Keywords: synovial fluid, biomarkers, cytokines, proteomics, metabolomics, extracellular vesicles

1. Introduction

Arthritis remains a major cause of pain and disability worldwide. Although synovial fluid (SF) analysis is already essential in determining cell counts, crystal identification, and microbiology, its molecular content is still underused in routine care worldwide[1,2,3] .

Compared with blood, synovial fluid better reflects local inflammatory activity, matrix turnover, and tissue remodeling [4]. The challenge is not whether the fluid is informative, but which measurements are specific, reproducible, and likely to change management.

Traditionally, synovial fluid analysis has focused on leukocyte count, differential cell analysis, crystal identification, Gram staining, glucose levels, and microbiological cultures[5,6]. These techniques remain fundamental for distinguishing inflammatory, septic, and crystal-induced arthritis; however, they provide limited insight into molecular disease mechanisms and prognostic heterogeneity.

SF represents a direct biochemical reflection of the intra-articular microenvironment and therefore provides unique information regarding local inflammatory activity, cartilage degradation, angiogenesis, oxidative stress, and immune activation [7,8].

Compared with serum biomarkers, SF-derived biomarkers are less influenced by systemic physiological variation and may therefore provide greater specificity regarding local joint pathology [4].

Recent developments in proteomics, metabolomics, transcriptomics, extracellular vesicle research, and machine learning-assisted molecular analysis have transformed SF into a promising source of diagnostic and prognostic biomarkers. Emerging evidence suggests that integrated biomarker panels may distinguish inflammatory from degenerative arthritis, identify aggressive disease phenotypes, predict radiographic progression, and monitor therapeutic response.

This narrative review summarizes current evidence regarding conventional and emerging SF biomarkers across major diseases, discusses recent methodological advances, evaluates limitations of current research, and highlights future directions toward precision rheumatology.

2. Search Strategy

A narrative literature review was conducted using PubMed, Scopus, Web of Science, and Google Scholar to identify relevant publications on SF biomarkers in arthritis. Articles published between 2017 and 2026 were prioritized to capture contemporary work in proteomics, metabolomics, transcriptomics, extracellular vesicles, and machine learning-assisted biomarker research, while landmark older studies were retained when necessary to contextualize major concepts or historically important discoveries. Search terms included combinations of "synovial fluid biomarkers", "rheumatoid arthritis", "osteoarthritis", "psoriatic arthritis", "gout", "septic arthritis", "periprosthetic joint infection", "proteomics", "metabolomics", "microRNA", "extracellular vesicles", "cytokines", and "machine learning". Boolean operators and MeSH terms were used to broaden retrieval and improve precision. Priority was given to systematic reviews, narrative reviews, translational studies, observational cohort studies, and clinically relevant biomarker investigations. Particular emphasis was placed on inflammatory cytokines, matrix-degrading enzymes, extracellular vesicle-derived biomarkers, metabolomic profiles, transcriptomic signatures, and integrated multi-marker approaches. Studies focusing exclusively on serum biomarkers without SF analysis were generally excluded unless directly relevant to local intra-articular inflammatory mechanisms. Reference lists of selected articles were also screened manually to identify additional relevant studies not captured in the initial search. Because this is a narrative review, the methodology is inherently subject to selection bias and does not have the same level of reproducibility as a formal systematic review. This narrative review was prepared with consideration of the SANRA (Scale for the Assessment of Narrative Review Articles) recommendations in order to improve methodological transparency, literature selection, and overall reporting quality.

3. Synovial Fluid as a Diagnostic Tool

SF is a viscous ultrafiltrate of plasma produced by type A and type B synoviocytes within the synovial membrane. Under physiological

conditions, SF provides lubrication, nutrient transport, shock absorption, and maintenance of cartilage homeostasis [8].

Normal SF contains hyaluronic acid, lubricin, electrolytes, proteins, and small numbers of mononuclear cells. During inflammatory and degenerative joint diseases, substantial alterations occur in SF composition due to increased vascular permeability, infiltration of inflammatory cells, synovial hyperplasia, cartilage matrix degradation, oxidative stress, and cytokine release [7,9].

In rheumatoid arthritis (RA), SF becomes highly inflammatory and enriched with neutrophils, macrophages, cytokines, proteolytic enzymes, and autoantibodies [10]. In osteoarthritis (OA), although inflammation is generally less pronounced, elevated inflammatory mediators and degradative enzymes contribute significantly to cartilage destruction and pain generation [11,12].

Routine SF analysis traditionally includes macroscopic appearance and viscosity, leukocyte count and differential, crystal analysis using polarized microscopy, Gram stain and microbial culture, and protein and glucose measurements [5,6]. These conventional methods remain clinically indispensable. For example, neutrophil predominance strongly suggests inflammatory or septic arthritis, while monosodium urate and calcium pyrophosphate crystals establish the diagnosis of gout and pseudogout.

However, conventional cytological analysis alone cannot fully characterize the molecular pathways driving disease progression. As a result, high-throughput molecular technologies have emerged as valuable tools for detailed characterization of SF proteins, metabolites, lipids, nucleic acids, and extracellular vesicles [13-16]. Conventional SF testing remains essential for acute diagnostic assessment, whereas most molecular biomarkers remain investigational.

4. Cytokines and Inflammatory Biomarkers

Inflammatory cytokines are among the most extensively studied SF biomarkers because they directly reflect immune activation and synovial inflammation. Cytokine networks regulate leukocyte recruitment, angiogenesis, osteoclast activation, pannus formation, and extracellular matrix degradation [10,17].

IL-6 plays a central role in inflammatory arthritis and is strongly associated with synovial inflammation, disease activity, and radiographic progression

in RA [18,19]. SF IL-6 concentrations correlate with DAS28 and inflammatory markers and remain elevated, although typically to a lesser degree, in OA [11,12]. Despite its pathogenic and therapeutic relevance, IL-6 lacks sufficient specificity as an isolated diagnostic biomarker.

TNF- α is a central cytokine in RA and psoriatic arthritis (PsA) pathogenesis and contributes to chronic synovial inflammation, leukocyte recruitment, angiogenesis, cartilage destruction, and bone erosion [20,21,22]. Elevated SF TNF- α concentrations correlate with synovitis severity and radiographic progression in inflammatory arthritis. However, variable therapeutic response highlights the molecular heterogeneity of inflammatory arthritis and limits the utility of TNF- α as a standalone biomarker.

IL-1 β is a major pro-inflammatory cytokine involved in cartilage degradation, synovial inflammation, and activation of catabolic pathways in arthritis [12,23]. Elevated SF IL-1 β concentrations are observed in RA, OA, PsA, gout, and septic arthritis [23,24]. In gout, monosodium urate crystals activate the NLRP3 inflammasome, resulting in IL-1 β -driven neutrophilic inflammation [41]. Although biologically important, IL-1 β lacks disease specificity, and therapeutic targeting has produced mixed clinical results in OA and RA.

Elevated SF IL-8 levels are associated with increased neutrophil infiltration and synovial inflammation in RA, PsA, and septic arthritis [10,24].

CSF-1 is associated with macrophage activation, synovitis, cartilage degeneration, and structural progression in OA [12,25]. Because macrophage-driven inflammation is increasingly recognized as an important component of OA pathogenesis, CSF-1 has attracted interest as both a prognostic biomarker and potential therapeutic target. However, its clinical utility remains insufficiently validated.

Cytokines are sensitive markers of local inflammation but demonstrate substantial overlap across inflammatory, degenerative, and infectious arthritides. Their greatest potential clinical value lies in integrated biomarker panels and therapeutic-response stratification rather than standalone diagnosis. Measurement of inflammatory cytokines provides important information regarding disease activity, severity of synovial inflammation, risk of disease flare, therapeutic response, and prognostic stratification [17,19].

5. Proteomics and Matrix-Degrading Enzymes

Proteomics enables comprehensive evaluation of proteins involved in inflammation, extracellular matrix remodeling, cartilage degradation, oxidative stress, angiogenesis, and tissue repair [13,26]. Recent advances in liquid chromatography-tandem mass spectrometry (LC-MS/MS) have significantly expanded understanding of SF protein composition.

Matrix metalloproteinases (MMP) are key mediators of extracellular matrix degradation and structural joint damage in arthritis [12,27]. Among them, MMP-3 and MMP-13 are the most extensively studied SF biomarkers.

MMP-3 reflects synovial fibroblast activation and inflammatory activity and correlates with synovitis severity, radiographic progression, and treatment response in RA [27,28]. In OA, elevated MMP-3 levels are also associated with cartilage degradation, although concentrations are generally lower than in RA.

MMP-13 plays a more direct role in degradation of type II collagen and is strongly associated with cartilage destruction and OA progression [29]. Because MMP-13 expression may occur early in disease, it has attracted interest as a potential marker of early cartilage degeneration.

TIMP-1 is a natural inhibitor of MMP and contributes to regulation of extracellular matrix turnover. Altered MMP/TIMP balance is associated with progressive structural damage in both RA and OA [30]. Elevated SF TIMP-1 concentrations likely represent a compensatory response to increased matrix degradation; however, TIMP-1 alone lacks sufficient specificity for routine clinical use.

VEGF promotes synovial angiogenesis and correlates with inflammatory activity, pannus formation, and disease severity in RA and PsA [20,21]. Although biologically informative, VEGF lacks disease specificity and remains primarily investigational.

Among proteomic markers, MMP-3 currently demonstrates the clearest association with active synovitis and treatment monitoring, whereas MMP-13 is more closely linked to cartilage degradation. VEGF and TIMP-1 are biologically informative but demonstrate limited disease specificity.

Recent advances in proteomics have shifted attention from isolated biomarkers toward integrated multi-protein signatures capable of reflecting the biological heterogeneity underlying arthritis. Proteomic analyses have also shown that inflammatory OA phenotypes may resemble

RA more closely than previously recognized, particularly regarding cytokine activation and neutrophil-associated pathways [11].

High-throughput mass spectrometry has further enabled identification of candidate biomarkers associated with complement activation, lipid metabolism, extracellular matrix remodeling, oxidative stress, and synovial angiogenesis.

Integrated proteomic profiling may improve molecular characterization of arthritis; however, current applications remain primarily investigational and lack sufficient standardization for routine clinical use.

6. Extracellular Vesicles and Exosome Biomarkers

Exosomes isolated from OA SF contain proteins associated with cartilage degradation, oxidative stress, and extracellular matrix remodeling. Additionally, exosome-derived microRNAs regulate inflammatory signaling pathways and cartilage metabolism [16,31]. In inflammatory arthritis, SF EVs arise from multiple cellular sources, including fibroblast-like and macrophage-like synoviocytes, chondrocytes, activated T cells and monocytes, and platelets; their surface tetraspanins (CD9, CD63, CD81) and vesicular cargo—non-coding RNAs (including miR-146a and miR-155), heat shock proteins, complement components, and matrix-degrading enzymes—broadly reflect this cell of origin and the local inflammatory state, with synoviocyte-derived EVs predominating in rheumatoid synovitis and chondrocyte-derived EVs more prominent in osteoarthritic cartilage turnover [32]. Isolating EVs from SF is technically demanding because of the fluid's high viscosity, which stems from its dense hyaluronic acid and lubricin content. Differential ultracentrifugation, the most widely used isolation method, co-purifies substantial non-vesicular contaminants—serum albumin, immunoglobulins, high-density lipoproteins, and extracellular matrix fragments—that can confound downstream proteomic and functional analyses; size-exclusion chromatography improves purity but adds cost, processing time, and inter-laboratory variability, and no isolation protocol has yet been standardized specifically for SF [44]. Although extracellular vesicles-derived biomarkers demonstrate diagnostic and mechanistic potential, this methodological variability and limited standardization currently restrict clinical implementation.

7. MicroRNAs and Genetic Biomarkers

MicroRNAs (miRNAs) are short non-coding RNAs involved in post-transcriptional regulation of gene expression. Because miRNAs remain

relatively stable in biological fluids, they have emerged as attractive biomarker candidates in rheumatologic diseases [16,32].

miR-146a is one of the best-characterized microRNAs in inflammatory arthritis and regulates NF- κ B-associated inflammatory signaling pathways [32]. Elevated SF miR-146a levels correlate with inflammatory activity, synovial hyperplasia, and cytokine expression in RA. Although increased expression may represent a compensatory anti-inflammatory response, it appears insufficient to suppress chronic inflammation fully.

miR-155 is a pro-inflammatory microRNA associated with macrophage activation, cytokine production, and persistent synovitis [32,33]. Increased expression has been reported in RA and PsA and correlates with inflammatory activity and cytokine release. Experimental studies suggest that miR-155 contributes to osteoclast activation and structural damage.

miR-140 is strongly associated with cartilage homeostasis and extracellular matrix regulation in OA [33]. Reduced SF miR-140 expression correlates with cartilage degeneration and disease progression and may occur early in OA development. Although miR-140 has attracted interest as a potential biomarker and therapeutic target, current evidence remains largely experimental.

8. Metabolomics and Multi-Omics Approaches

Metabolomics involves large-scale analysis of small molecules generated during cellular metabolism [7,14]. Because inflammatory and degenerative joint diseases alter metabolic activity inside the intra-articular environment, metabolomic profiling provides valuable insight into disease mechanisms. Altered SF concentrations of lactate, amino acids, lipid metabolites, and oxidative stress markers have been identified in both OA and RA [7,14].

8.1 Lactate

Elevated SF lactate concentrations reflect anaerobic metabolism and hypoxic synovial environments associated with intense inflammatory activity [34]. During severe synovial inflammation, increased leukocyte infiltration and local tissue hypoxia stimulate anaerobic glycolysis, resulting in lactate accumulation within the joint cavity. Increased lactate levels are commonly observed in septic arthritis and severe inflammatory synovitis. Because bacterial infection additionally contributes to metabolic dysregulation and neutrophil activation, lactate levels may assist in the differentiation between infectious and noninfectious arthritis. Several

studies suggest that markedly elevated SF lactate concentrations demonstrate favorable sensitivity for septic arthritis, particularly when interpreted together with leukocyte count and microbiological findings. D-lactate has attracted additional interest because it is produced predominantly through bacterial metabolism rather than host cellular activity. As a result, D-lactate may potentially provide greater specificity for bacterial infection compared with total lactate alone. Elevated lactate concentrations are not exclusive to septic arthritis and may additionally occur in severe inflammatory arthritides such as RA or crystal-induced arthritis. Despite this promise, lactate and D-lactate measurement is not yet incorporated into most routine SF diagnostic panels, and proposed cut-off values vary across studies depending on the analytical platform and patient population, underscoring the need for assay standardization before broader clinical adoption.

8.2 Lipid Metabolites

Changes in lipid metabolism contribute to inflammatory signaling, membrane instability, oxidative stress, and cellular dysfunction within arthritic joints [12,35]. Altered phospholipid, sphingolipid, cholesterol, and fatty acid profiles have been identified in both OA and RA. Certain phospholipid and sphingolipid species have been associated with cartilage degeneration, synovitis severity, and pain burden. Specific lysophosphatidylcholine, lysophosphatidic acid, ceramide, and sphingosine-1-phosphate species have been implicated in pain signaling and catabolic chondrocyte responses, while cholesterol accumulation within synoviocytes contributes to activation of inflammatory pathways such as the NLRP3 inflammasome. Altered lipidomic profiles have been associated with synovitis severity, cartilage degeneration, and inflammatory activity in both OA and RA [12,35]. Because lipidomic assays require specialized mass spectrometry infrastructure and standardized pre-analytical handling to prevent lipid degradation, these markers remain confined largely to research settings.

8.3 Amino Acid Profiles

Altered amino acid metabolism reflects inflammatory activation, oxidative stress, and tissue remodeling within arthritic joints [7]. Changes in glutamine, arginine, tryptophan, and branched-chain amino acid metabolism have been described in both RA and OA. These alterations may reflect immune-cell activation, cartilage catabolism, and metabolic stress; for example, glutamine depletion has been linked to heightened synovial lymphocyte and macrophage activity, while reduced branched-chain amino

acid concentrations parallel cartilage catabolic turnover in OA. However, amino acid profiles are strongly influenced by obesity, diet, medication exposure, and systemic metabolic factors, limiting current clinical applicability.

8.4 Multi-Omics Integration and Machine Learning

Integrated multi-omics approaches combine cytokine profiling, proteomics, metabolomics, transcriptomics, imaging findings, and clinical data to better characterize the biological heterogeneity underlying arthritis [14,15,16,30,36]. Early studies suggest that machine learning-assisted analyses can improve arthritis classification, identification of inflammatory phenotypes, and prediction of disease progression or therapeutic response compared with conventional biomarker assessment [30,36]. Although current applications remain largely investigational, integrated multi-omics approaches represent one of the most promising future directions in precision rheumatology.

Table 1 summarizes the major synovial fluid biomarker categories in inflammatory arthritis, including cytokines, matrix remodeling enzymes, microRNAs, metabolites, extracellular vesicles, and multi-protein signatures, together with their principal pathophysiological roles and potential clinical applications.

Table 1. Major Synovial Fluid Biomarkers and Their Clinical Relevance in Arthritis.

Biomarker Category	Examples	Main Pathophysiological Role	Diseases Associated	Potential Clinical Utility	References
Cytokines/Chemokines	IL-6, TNF- α , IL-1 β , IL-17, IL-8	Immune activation, synovitis, cytokine amplification	RA, PsA, OA, septic arthritis, gout	Disease activity assessment, prognosis, therapeutic monitoring	[17,18,20,23]
Matrix remodeling enzymes	MMP-3, MMP-13, ADAMTS-5	Extracellular matrix degradation, cartilage destruction	RA, OA, PsA	Prediction of structural progression, monitoring cartilage damage	[26,27,29,35]
Matrix inhibitors	TIMP-1	Regulation of extracellular matrix turnover	RA, OA	Evaluation of MMP/TIMP balance and tissue remodeling	[26,27]

Angiogenic mediators	VEGF	Synovial angiogenesis, vascular proliferation	RA, PsA, OA	Assessment of inflammatory severity and pannus formation	[20,21]
Macrophage-associated markers	CSF-1, calprotectin	Macrophage activation, innate immune signaling	OA, RA, septic arthritis	Identification of inflammatory phenotypes	[9,12,25]
MicroRNAs	miR-146a, miR-155, miR-140	Post-transcriptional immune and cartilage regulation	RA, OA, PsA	Disease stratification, treatment response prediction	[16,32,33]
Metabolites	Lactate, lipid metabolites, amino acids	Metabolic reprogramming, oxidative stress	Septic arthritis, RA, OA, gout	Diagnostic support and metabolomic profiling	[7,34,35]
Extracellular vesicle biomarkers	Exosomal proteins and miRNAs	Intercellular signaling and inflammatory regulation	RA, OA, PsA	Precision medicine and molecular phenotyping	[15,31,32]
Multi-protein signatures	Integrated cytokine/proteomic panels	Complex inflammatory and degradative pathways	RA, OA, PsA	Improved diagnostic and prognostic accuracy	[26,30,36]
Genetic/Epigenetic markers	HLA alleles, DNA methylation patterns	Genetic susceptibility and immune dysregulation	RA, PsA, CTD-associated arthritis	Molecular stratification and personalized medicine	[16,33]

Abbreviations: ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs 5; CSF-1, colony-stimulating factor 1; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; IL-17, interleukin-17; miRNAs (incl. miR-146a, miR-155, miR-140), microRNAs; MMP-3, matrix metalloproteinase-3; MMP-13, matrix metalloproteinase-13; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TIMP-1, tissue inhibitor of metalloproteinases-1; TNF- α , tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

9. Biomarkers in Specific Arthritides

9.1 Rheumatoid Arthritis

RA demonstrates one of the most extensively characterized synovial fluid biomarker profiles among inflammatory arthritides [10,18]. Elevated SF concentrations of IL-6, TNF- α , IL-1 β , MMP-3, RF, and anti-CCP antibodies

correlate with active synovitis, radiographic progression, and disease severity [18,19,27].

MMP-3 is considered one of the most clinically relevant SF biomarkers in RA because it reflects synovial fibroblast activation and extracellular matrix degradation. Elevated MMP-3 levels correlate with radiographic progression and may decrease following successful biologic therapy, supporting its potential role in treatment monitoring [27,28].

Autoantibody analysis within SF may provide insight into local autoimmune activation. Anti-CCP antibodies detected in SF may reflect intra-articular immune activity, while local immune complex formation and synovial B-cell activation contribute to persistent inflammation [10,18]. Recent transcriptomic studies suggest substantial molecular heterogeneity in RA inflammatory pathways [15,16,31].

9.2 Osteoarthritis

Synovial inflammation, macrophage activation, oxidative stress, metabolic dysregulation, and extracellular matrix degradation all contribute to disease progression. Elevated SF concentrations of IL-6, IL-1 β , MMP-13, ADAMTS-5, CSF-1, and exosome-derived proteins reflect cartilage degradation and synovial inflammation and have been associated with structural damage, pain severity, synovitis, and functional limitation [11,12,29]. MMP-13 and ADAMTS-5 contribute to cartilage degradation and structural progression in OA [29]. Macrophage-driven inflammation has also emerged as an important pathogenic component of OA. Elevated CSF-1 concentrations correlate with macrophage activation and synovial hypertrophy, supporting the contribution of innate immune mechanisms to disease progression [25]. Several studies have identified inflammatory OA phenotypes characterized by elevated IL-6, TNF- α , and neutrophil-associated biomarkers resembling inflammatory arthritis [9,11]. Current evidence also suggests that metabolic inflammation associated with obesity contributes to distinct inflammatory OA phenotypes characterized by increased synovial expression of pro-inflammatory cytokines and matrix-degrading enzymes, further supporting the potential use of SF inflammatory biomarkers for patient stratification and monitoring disease progression [37,38].

9.3 Psoriatic Arthritis

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease characterized by synovitis, enthesitis, dactylitis, axial inflammation, and pathological bone remodeling. Available data indicate that SF biomarker

profiles in PsA differ from both RA and OA, although overlap exists [10,21]. Elevated concentrations of TNF- α , IL-17, IL-23, IL-22, and IL-8 have been consistently identified within PsA SF and contribute to synovial inflammation, osteoclast activation, angiogenesis, and enthesial pathology. Elevated SF IL-17 concentrations have additionally been associated with active enthesitis and erosive disease. Increased VEGF concentrations may contribute to synovial vascular proliferation and persistence of chronic inflammation. Proteomic studies have identified disease-specific exosomal and protein signatures in PsA synovial fluid. Certain inflammatory proteins and extracellular vesicle-associated molecules may assist differentiation between PsA and RA, particularly in seronegative patients with overlapping clinical manifestations [15,31].

9.4 Septic Arthritis and Periprosthetic Joint Infection (PJI)

Distinguishing septic arthritis from inflammatory or crystal-induced arthritis may be clinically challenging, particularly during early disease stages. Traditional diagnostic methods include leukocyte count, Gram stain, glucose measurement, and microbiological culture; however, these approaches demonstrate important limitations. Culture results may be delayed or falsely negative, while elevated leukocyte counts may occur in both infectious and noninfectious inflammatory arthritides. Among the emerging SF biomarkers proposed to address these gaps—including alpha-defensin, presepsin, lactate, D-lactate, calprotectin, procalcitonin, and synovial CRP—alpha-defensin has become one of the most extensively investigated in PJI diagnosis [39,40]. Alpha-defensins are antimicrobial peptides released by activated neutrophils in response to bacterial pathogens. Multiple investigations have demonstrated high specificity for PJI, particularly when combined with leukocyte esterase testing and synovial CRP. Despite this, alpha-defensin does not achieve perfect diagnostic accuracy. False-positive results may occur in severe inflammatory arthritis, metallosis, or crystal-induced inflammation. As a result, current evidence supports interpretation of alpha-defensin within broader diagnostic algorithms rather than as an isolated definitive test. D-lactate additionally represents a promising biomarker because it is produced primarily by bacterial metabolism rather than host tissues [46]. Elevated SF D-lactate concentrations may therefore assist differentiation between septic and noninfectious inflammatory arthritis. Presepsin, a soluble CD14 subtype released during bacterial activation of monocytes and macrophages, has also attracted interest as a rapid biomarker for septic arthritis. Preliminary studies suggest potentially favorable sensitivity and specificity; however, validation continues to be restricted. In native septic

arthritis, neutrophil-associated cytokines and inflammatory mediators such as IL-8 and calprotectin may additionally correlate with infection severity and inflammatory burden. Despite substantial progress, no single SF biomarker currently replaces conventional microbiological analysis and clinical assessment. Therefore, multimodal diagnostic approaches integrating biomarkers, culture results, imaging findings, and clinical presentation remain essential.

9.5 Crystal-Induced Arthritis

Crystal-induced arthritides, including gout and calcium pyrophosphate deposition disease (CPPD), continue to be diagnosed primarily through the detection of monosodium urate or calcium pyrophosphate crystals by polarized light microscopy [5,6]. Nevertheless, analysis of synovial fluid biomarkers may provide complementary information regarding the intensity of local inflammation and may be useful when distinguishing crystal-induced flares from septic arthritis is challenging. In gout, deposition of monosodium urate crystals triggers activation of the NLRP3 inflammasome, resulting in increased IL-1 β production and a predominantly neutrophil-driven inflammatory response [41]. Acute attacks are also associated with increased levels of pro-inflammatory mediators such as IL-6, TNF- α , IL-8, and calprotectin, reflecting activation of innate immune pathways within the joint [10,24,41]. Comparable inflammatory mechanisms have been described in CPPD, although the available evidence regarding specific synovial fluid biomarkers is considerably less extensive [10]. Despite growing interest in these molecular markers, none currently demonstrate sufficient diagnostic specificity to replace crystal identification, and their principal role remains the assessment of inflammatory activity rather than establishing a definitive diagnosis [5,6,41].

9.6 Connective Tissue Disease-Associated Arthritis

Emerging evidence suggests that SF biomarkers may also contribute to characterization of connective tissue disease-associated arthritis [42,43]. In systemic lupus erythematosus (SLE) and related connective tissue diseases, SF biomarkers are less validated than in RA or PsA, but IL-17A, IL-6, and immune-complex-related signatures suggest local inflammatory activity that should be interpreted alongside systemic serology and phenotype [43]. Cellular studies of SLE synovial fluid have additionally identified an expansion of CCR6-expressing CD4⁺ T cells with a Th17-skewed phenotype, together with elevated frequencies of granzyme A- and Eomes-expressing CD8⁺ T cells, suggesting that lupus arthritis reflects a systemic Th17-

associated immune deviation rather than a joint-specific autoimmune process analogous to RA [43]. Because SLE arthritis is typically non-erosive and clinically less destructive than RA, and because comparably sized SF cohorts are difficult to assemble given the low frequency of arthrocentesis in SLE, biomarker signatures for other connective tissue disease-associated arthritides, including Sjögren's syndrome and systemic sclerosis, remain considerably less characterized and represent an area requiring dedicated prospective study.

9.7 Lyme Arthritis

Lyme arthritis, a late manifestation of infection with *Borrelia burgdorferi*, most commonly presents as monoarthritis or oligoarthritis of the knee and can mimic septic or crystal-induced arthritis both clinically and on conventional SF analysis. Direct detection of *B. burgdorferi* DNA by polymerase chain reaction in SF supports diagnosis in a substantial proportion of patients and remains more sensitive than culture, although a negative result does not exclude the diagnosis, particularly after antibiotic exposure [45]. Serum and SF anti-borrelial antibody testing (two-tier serology) remains the diagnostic mainstay, but SF biomarkers may assist when serology is equivocal or when distinguishing Lyme arthritis from septic arthritis is clinically urgent. Elevated SF alpha-defensin (human neutrophil peptides 1–3) concentrations have been reported in Lyme arthritis, reflecting neutrophil activation in response to spirochetal infection; because these levels can overlap with those seen in bacterial PJI and severe inflammatory arthritis, alpha-defensin elevation in Lyme arthritis should be interpreted together with epidemiological exposure, serology, and PCR findings rather than in isolation [42]. Compared with RA, OA, and PJI, the SF biomarker literature specific to Lyme arthritis remains limited, and further studies are needed to define its cytokine and proteomic signature relative to other inflammatory and infectious arthritides.

Although these biomarkers are not yet routinely used clinically, they highlight disease-specific inflammatory pathways and may contribute to future molecular stratification. Figure 1 shows the evolution of synovial fluid biomarkers.

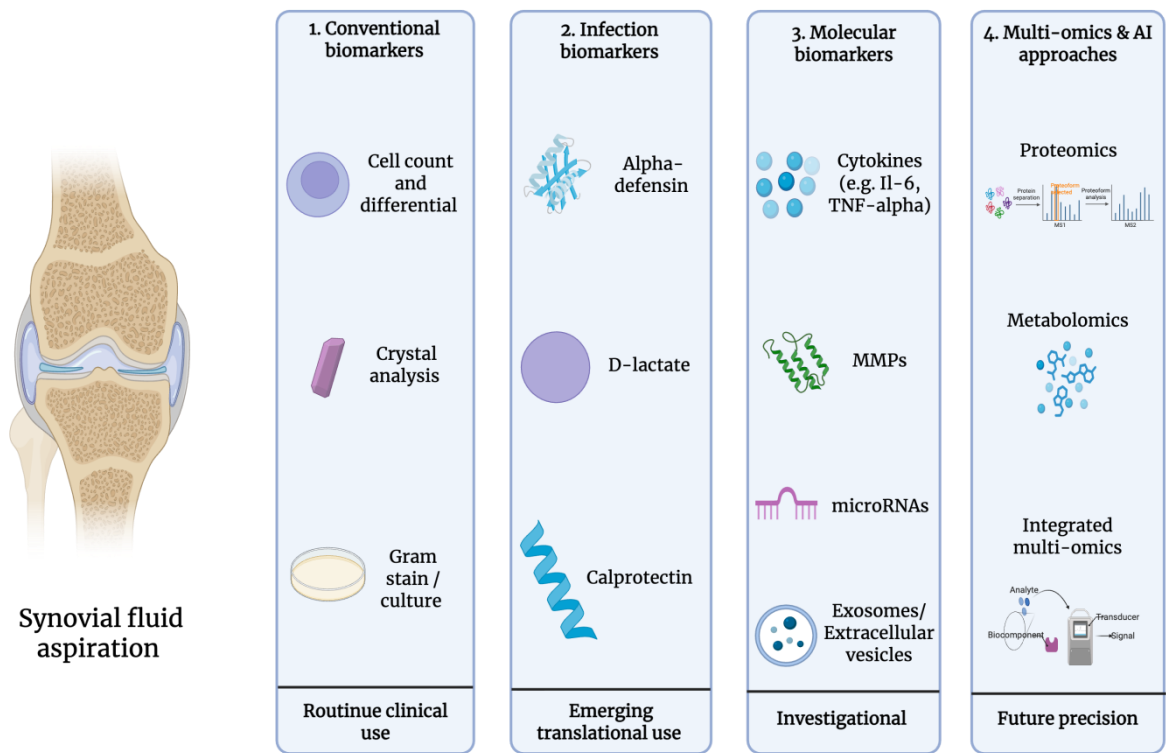


Figure 1. Evolution of Synovial Fluid Biomarkers.

10. Clinical Applications and Future Perspectives

The central shift in synovial fluid biomarker research is no longer whether SF is biologically informative, but which biomarkers provide clinically actionable information beyond conventional assessment. The clearest near-term clinical utility is in infection-oriented applications, particularly septic arthritis and PJI, where biomarkers such as D-lactate and alpha-defensin may complement leukocyte count, microbiological culture, and conventional synovial fluid analysis to improve diagnostic triage and early therapeutic decision-making [34,40,39,46].

Viewed comparatively, biomarker readiness for clinical use varies substantially across the diagnostic performance, prognostic utility, and validation dimensions summarized in Table 1. Alpha-defensin has the strongest evidence base of any single SF biomarker, with high reported specificity for PJI in multiple cohorts, though its diagnostic performance falls short of a stand-alone test because of false positives in metallosis and severe inflammatory arthritis; it is best regarded as validated for a narrow,

well-defined clinical question (infection versus aseptic loosening) rather than as a general-purpose marker. D-lactate, calprotectin, and presepsin occupy an intermediate tier: mechanistically plausible and consistent across smaller cohorts, but lacking the multicenter validation and standardized cut-offs needed for routine adoption. Cytokines (IL-6, TNF- α , IL-1 β , IL-17) and matrix-degrading enzymes (MMP-3, MMP-13) have the deepest mechanistic literature and clear prognostic associations with radiographic progression, but their limited disease specificity means they function better as components of composite activity or treatment-response panels than as diagnostic tests in isolation; IL-6 and MMP-3 in particular are shared across RA, PsA, and OA and therefore discriminate inflammatory intensity rather than diagnosis. Extracellular vesicles, microRNAs, and metabolomic and lipidomic panels remain the least clinically mature tier: individually informative and mechanistically rich, but constrained by methodological variability (Section 6), absence of standardized isolation and reporting protocols, and a near-total lack of prospective validation cohorts, which are the principal factors currently limiting their transition from investigational tool to clinical assay. This tiered picture - one validated infection-specific test, several intermediate infection and inflammation markers awaiting standardization, a mechanistically rich but non-specific cytokine/protease layer, and an investigational omics layer—frames the translational priorities discussed below.

In contrast, for RA, PsA, and OA, most cytokines, proteases, and molecular biomarkers improve inflammatory phenotyping and prognostic stratification rather than providing disease-specific diagnostic certainty. Multi-omics integration and machine learning-assisted analyses remain particularly promising because they may capture the biological heterogeneity underlying clinically similar arthritis phenotypes [14,15,16,30,36]. For instance, in a patient with established RA, such an approach might in principle help distinguish a flare of uncontrolled inflammatory disease activity from superimposed secondary OA, though this specific application has not yet been directly validated and remains a hypothesis for future study rather than an established capability.

At present, the most practical translational strategy is a stepwise multimodal approach: conventional SF analysis for initial triage, selective incorporation of targeted biomarkers when clinically relevant questions arise, and future integration of validated multi-omics models for molecular stratification and rheumatology applications.

Translating this stepwise strategy into routine hospital practice, however, requires an honest appraisal of cost and infrastructure. Mature markers such as alpha-defensin, lactate, and calprotectin are compatible with existing lateral-flow, ELISA, or automated chemistry platforms already present in most clinical laboratories, and their per-sample cost and turnaround time are comparable to routine inflammatory markers. In contrast, high-throughput mass spectrometry-based proteomics and RNA sequencing require substantial capital investment in instrumentation, specialized bioinformatics support, and quality-control infrastructure that remain concentrated in a small number of academic or reference centers [13,36]. Within European healthcare systems, and particularly in Bulgaria and other countries with more limited public laboratory budgets, this translates into restricted geographic access, longer turnaround times, and reimbursement pathways that are not yet defined for omics-based SF testing. Consequently, mature biomarkers are likely to remain the pragmatic first-line tools for the foreseeable future, while omics panels are best positioned as centralized reference-laboratory or research tools for complex or diagnostically ambiguous cases, with eventual broader adoption contingent on falling sequencing and instrumentation costs, simplified sample-to-answer workflows, and formal cost-effectiveness data relative to conventional testing.

11. Limitations and Challenges

Despite substantial progress, most SF biomarkers remain insufficiently validated for routine clinical use. Major limitations include biological overlap between arthritides, variability in sample handling and analytical methods, limited reproducibility across studies, and the high cost and technical complexity of omics-based approaches [4,14,15,16,30,36]. Future progress will depend on multicenter validation, assay standardization, and demonstration of incremental clinical value beyond conventional SF analysis.

A principal strength of this narrative review is its broad disease scope, spanning not only the major inflammatory and degenerative arthritides but also less commonly reviewed entities such as Lyme arthritis and connective tissue disease-associated arthritis, together with an integrated treatment of conventional, proteomic, metabolomic, extracellular vesicle, microRNA, and multi-omics biomarkers within a single framework. This breadth allows direct comparison of biomarker maturity across diseases, which is rarely attempted in narrower disease-specific reviews. The principal limitations are inherent to the narrative format: literature selection was not conducted

according to a pre-registered systematic protocol and is therefore susceptible to selection bias; searches were restricted to English-language databases, which may have excluded relevant regional or non-English literature; and the qualitative synthesis of heterogeneous study designs, patient populations, and analytical platforms does not permit formal quantitative pooling of diagnostic accuracy across studies.

Beyond these methodological considerations, several clinical limitations intrinsic to SF sampling itself constrain biomarker research and its translation. Non-effusive or minimally effusive joints frequently yield a "dry tap," precluding SF collection altogether and biasing available samples toward more severely inflamed joints. Obtaining genuinely healthy control SF for baseline omics comparisons is ethically and logistically difficult, since arthrocentesis is not performed on asymptomatic joints without clinical indication; consequently, many "control" samples are in fact derived from patients undergoing joint surgery or arthroscopy for unrelated mechanical indications, which may not fully represent a biomarker-naïve baseline. Finally, systemic comorbidities—including obesity, diabetes, and chronic kidney disease—can alter local joint metabolism and inflammatory tone independently of the primary articular disease, potentially confounding SF biomarker interpretation unless these factors are explicitly accounted for in study design and analysis.

12. Conclusion

SF biomarkers are increasingly recognized as useful adjuncts for diagnosis, inflammatory phenotyping, and therapeutic monitoring in arthritis. Among currently available biomarkers, alpha-defensin demonstrates the strongest clinical utility, particularly in PJI, while D-lactate, calprotectin, MMP-3 and MMP-13 show emerging translational relevance. Most proteomic, metabolomic, extracellular vesicle, and microRNA-based biomarkers remain investigational because of limited validation and standardization. Future progress will likely depend on integrated multimodal approaches combining molecular biomarkers with imaging and clinical assessment rather than reliance on isolated analytes.

Declarations

Author Contributions

Author Contributions: Conceptualization: V.T.; Methodology: M.I., V.T.; Writing - original draft preparation: V.T.; Visualisation: V.T., S.T.; Writing - review and editing: M.I., G.K., V.T.

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No new data was generated in the study.

Conflicts of Interest

The authors declare no conflict of interest.

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Биомаркери в синовиалната течност: настоящи приложения и бъдещи перспективи

Резюме

Синовиалната течност предоставя директен поглед към вътреставната среда, но отделните биомаркери рядко разграничават надеждно подтиповете артрит. Настоящият наративен обзор сравнява конвенционалните изследвания с цитокини, протеомични маркери, извънклетъчни везикули, микроРНК, метаболомика и мултиомика, подпомогната от машинно обучение, при ревматоиден артрит, остеоартрит, псориаатичен артрит, септичен артрит, перипротезна ставна инфекция, кристал-индуциран артрит, артрит, свързан със заболявания на съединителната тъкан, и Лаймски артрит. Релевантните публикации от периода 2017–2026 г. бяха идентифицирани чрез структурирани търсения в базите данни PubMed, Scopus, Web of Science и Google Scholar, допълнени от ръчен преглед на библиографските списъци; при селекцията бяха приоритизирани систематични и наративни обзори, транслационни проучвания и клинично значими изследвания на биомаркери, като докладването следва рамката SANRA за наративни обзори. Най-утвърдените в клиничната практика приложения остават конвенционалното определяне на клетъчния брой, анализът на кристали, микробиологичното изследване и оценката на алфа-дефензин при перипротезни ставни инфекции, докато изследването на извънклетъчните везикули, микроРНК и мултиомиката запазват предимно транслационния си характер.

Ключови думи: синовиална течност, биомаркери, цитокини, протеомика, метаболомика, извънклетъчни везикули