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The role of serum inflammatory biomarkers in the timely and accurate diagnosis of periprosthetic joint infections

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Abstract

Periprosthetic joint infection (PJI) is a major complication in arthroplasty, where rapid and accurate diagnosis is critical to preserving prosthetic function and reducing morbidity. PJI triggers innate immune activation, cytokine release, and acute-phase protein production, leading to measurable serum biomarker changes. Acute PJIs typically show marked elevations in C-reactive protein (CRP) and interleukin-6 (IL-6), whereas chronic biofilm associated infections present with attenuated responses. Conventional biomarkers—CRP, erythrocyte sedimentation rate (ESR), and WBC count—remain first-line tests, each with distinct kinetics, thresholds, and limitations. Novel biomarkers such as IL-6, procalcitonin (PCT), D-dimer, and presepsin, as well as cytokines like TNF-α and IL-1β, may offer superior diagnostic performance, particularly when traditional results are inconclusive. Comparative studies and meta analyses show high sensitivity for CRP and IL 6 in acute settings, while D dimer and presepsin add value in selected cases. Combining biomarkers—especially CRP with IL-6—can achieve sensitivities and specificities above 90–95%. Importantly, low grade infections from organisms such as *Cutibacterium acnes* may yield near normal systemic markers, highlighting the role of adjunctive synovial fluid analysis. Overall, both traditional and emerging serum biomarkers are indispensable when incorporated into a multimodal diagnostic strategy, enhancing timely and accurate PJI detection.

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Introduction

Periprosthetic joint infection (PJI) is one of the most serious and challenging complications following joint arthroplasty, representing a major cause of morbidity, revision surgery, and long-term functional impairment (1,2). Defined as an infection involving the joint prosthesis and surrounding tissues, PJI can lead to devastating clinical consequences if not promptly and accurately diagnosed (3). Timely identification is critical, as early intervention significantly improves the likelihood of successful infection eradication, prosthesis retention, and functional recovery. Delay in diagnosis, conversely, often results in more extensive surgical interventions, protracted antibiotic courses, and reduced rates of limb preservation (4).

The epidemiology of PJI varies according to the joint involved and the type of prosthesis. Current literature estimates an incidence of approximately 1–2% following primary total hip arthroplasty and 1–2% after total knee arthroplasty, with higher rates reported in revision procedures, trauma-related arthroplasty, and in patients with significant comorbidities (5). Although less frequent in shoulder, elbow, or ankle arthroplasties, PJIs in these joints present unique diagnostic and therapeutic challenges, often compounded by atypical microbiological profiles and subtler clinical presentations (6). With the global rise in the number of arthroplasties performed annually, the absolute number of PJIs is projected to increase, further amplifying the need for accurate and timely diagnostic strategies (7).

The consequences of delayed or missed PJI diagnosis are both clinically and economically significant. Clinically, late-stage infections often require staged revision arthroplasties, prolonged hospital stays, and aggressive antimicrobial therapy, all of which carry a high burden for patients (8). Functionally, these patients frequently experience diminished mobility, persistent pain, and decreased quality of life. Economically, PJIs impose a substantial financial strain on healthcare

Key point

Timely periprosthetic joint infection (PJI) diagnosis relies on integrating conventional and novel serum biomarkers. We found, C-reactive protein (CRP) and interleukin-6 (IL-6) in acute cases, while D dimer, presepsin, tumor necrosis factor-alpha (TNF-α), and IL 1β help in equivocal or chronic presentations. Combining markers improves sensitivity and specificity, supporting a multimodal, subtype aware diagnostic approach.

systems, with some estimates indicating treatment costs exceeding $50,000 per case in high-income countries. Furthermore, recurrent infections and multiple surgeries compound these costs and consume significant hospital resources (9).

Within the diagnostic algorithm of PJI, serum inflammatory biomarkers have emerged as essential tools for initial screening, treatment monitoring, and postoperative surveillance. Commonly employed biomarkers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count, serve as rapid, cost-effective, and minimally invasive means of assessing systemic inflammation (10). Emerging candidates such as procalcitonin (PCT), interleukin-6 (IL-6), and D-dimer have been investigated to improve diagnostic performance, particularly in challenging cases in which conventional biomarkers yield equivocal results. By integrating these markers into clinical decision-making, clinicians can increase diagnostic certainty, facilitate early intervention, and potentially reduce the need for invasive diagnostic procedures (11).

Despite their clinical value, current diagnostic approaches face important limitations. The sensitivity and specificity of conventional biomarkers vary, particularly in acute versus chronic PJI, in low-grade infections with low-virulence organisms, and in patients with concomitant inflammatory or autoimmune disorders (12). Diagnostic accuracy is also influenced by the temporal "window period" between symptom onset and biomarker elevation, which may lead to false-negative or inconclusive results in early infection stages. These limitations underscore the need for optimized biomarker panels, refined diagnostic thresholds, and integration with novel molecular or imaging modalities (13).

The rationale for the present review lies in addressing these persistent challenges by providing an updated synthesis of the evidence regarding serum inflammatory biomarkers in PJI diagnosis. By critically evaluating their diagnostic performance, exploring emerging candidates, and assessing their role in combination with other diagnostic modalities, this work aims to refine clinical algorithms and guide future research toward improving the timeliness and precision of PJI detection.

Material and Methods

A comprehensive literature search was conducted to identify relevant studies evaluating the role of serum inflammatory biomarkers in the diagnosis of PJIs. The search strategy incorporated keywords and Medical Subject Headings (MeSH) related to "periprosthetic joint infection," "serum biomarkers," "inflammation," "C-reactive protein," "erythrocyte sedimentation rate," "interleukins," and "diagnostic accuracy." Electronic databases, including PubMed, Scopus, Web of Science, and Embase, were systematically searched without time restrictions, and only studies published in English were considered. The search was supplemented by manual screening of reference lists from retrieved articles to ensure comprehensive inclusion of pertinent literature.

Results

Pathophysiology and mechanisms

Host immune inflammatory response to prosthetic joint infection

When a PJI occurs, the host immune system mounts a complex inflammatory response aimed at eliminating invading pathogens while minimizing collateral tissue damage. Bacterial adhesion to the prosthetic surface triggers the formation of biofilms, which shield pathogens from phagocytosis and antimicrobial penetration (14). The immune system detects pathogen-associated molecular patterns by pattern-recognition receptors such as Toll-like receptors on macrophages, neutrophils, and dendritic cells. This recognition rapidly activates innate immunity and initiates recruitment of neutrophils and monocytes to the infected site, leading to phagocytic clearance attempts, release of reactive oxygen species, and secretion of pro-inflammatory cytokines (15).

However, biofilm-associated infections often result in a state of persistent low-grade inflammation. As the pathogen evades eradication, inflammatory cells remain activated for prolonged periods, resulting in chronic immune stimulation and tissue destruction (16). The delicate balance between pathogen clearance and host tissue preservation becomes compromised, leading to osteolysis, loosening of the prosthesis, and progressive joint dysfunction. Understanding this immune response is essential for appreciating how serum inflammatory biomarkers reflect the underlying pathophysiology of PJI (17).

Activation pathways of inflammatory mediators (innate immunity, cytokine release, acute-phase reactants)

Innate immunity serves as the first line of defense in PJI, orchestrating a rapid but non-specific response via cellular and humoral mechanisms. Upon bacterial challenge, macrophages and dendritic cells release key cytokines such as interleukin-1β (IL-1β), IL-6, and TNF-α, which act locally to amplify inflammation and systemically to induce the hepatic acute-phase response (18). These pro-inflammatory mediators increase vascular permeability, enhance leukocyte adhesion to endothelium, and recruit additional immune cells to the site of infection. Complement activation further promotes opsonization

and direct bacterial lysis, reinforcing early microbial control efforts (19).

The hepatic acute-phase reaction is a defining systemic facet of PJI-related inflammation. Under the influence of IL-6 and other mediators, hepatocytes synthesize acute-phase proteins such as CRP, serum amyloid A and fibrinogen (20). These proteins serve diverse roles, including pathogen opsonization, modulation of immune cell activity, and alteration of coagulation pathways. Elevated circulating concentrations of these molecules serve as measurable biomarkers, reflecting ongoing systemic inflammation and aiding clinicians in the early recognition and monitoring of PJI (21).

Commonly used serum biomarkers

C-reactive protein

CRP is an acute-phase protein synthesized by hepatocytes in response to IL-6 stimulation, serving as a highly responsive marker of systemic inflammation (22). Following surgical implantation, CRP levels typically reach their physiological postoperative peak within 48–72 hours and decline rapidly, with a half-life of approximately 19 hours (23), provided no inflammatory complications occur (24). In the PJI diagnostic context, elevated CRP beyond the expected postoperative normalization window, or a secondary rise, is a key surgical red flag (25). Commonly recommended cut-off values for chronic PJI range from 10 to 20 mg/L, while acute infections often warrant higher thresholds, such as ≥100 mg/L, to account for normal postoperative inflammatory responses without compromising specificity (26).

In a narrative review, CRP demonstrates high sensitivity for acute PJI (84–98%) and moderate-to-high specificity (70–92%), making it a reliable screening tool in the early postoperative phase (27). Nevertheless, its diagnostic accuracy diminishes in chronic PJI, where low-grade infections may not appreciably elevate systemic CRP (28). Additional limitations include false positives in the presence of other inflammatory conditions (e.g., rheumatoid arthritis, inflammatory bowel disease) and transient rises after minor infections or trauma (29). Therefore, CRP should be interpreted in combination with other laboratory and clinical findings rather than as a stand-alone determinant (30).

Erythrocyte sedimentation rate

ESR is a non-specific but long-established marker that reflects aggregation of red blood cells under the influence of plasma proteins, particularly fibrinogen (26). After joint arthroplasty, ESR typically rises more slowly than CRP, peaking around postoperative day 5–7, and may remain persistently elevated for several weeks, even in the absence of infection (30). This kinetic profile makes ESR more valuable as a subacute-to-late phase indicator rather than as an immediate postoperative screening tool (31). In clinical practice, recommended ESR thresholds for PJI diagnosis are commonly set at ≥30 mm/h for knee prostheses and ≥20 mm/h for hip prostheses, though cut-offs vary across studies and guidelines (32).

While ESR provides useful diagnostic sensitivity for chronic PJI (often exceeding 90%), its specificity is comparatively modest, ranging from 60–80%, due to multiple confounding factors (33). Advanced age, anemia, malignancy, chronic kidney disease, and autoimmune disorders can elevate ESR in the absence of infection (29). Conversely, in acute high-grade infections, ESR may be normal in the earliest days post-infection onset (34). As with CRP, ESR interpretation benefits from integration into multimodal diagnostic algorithms, serving as a complementary marker that, when combined with CRP, improves overall diagnostic yield (32).

WBC count

Peripheral WBC count, widely used in systemic infection assessment, demonstrates limited diagnostic value in PJI (35). This limitation stems from the localized nature of many PJIs and the immune evasion strategies of biofilm-embedded bacteria, which may provoke minimal systemic leukocytosis (36). Reported sensitivities for WBC count in PJI are generally low (20–30%) while specificity can vary substantially, rendering it unreliable as a primary screening marker. A normal WBC count, therefore, does not exclude infection, particularly in chronic or indolent cases (37).

Several non-infectious and systemic infectious conditions can alter WBC levels, further undermining its utility in PJI diagnostics (38). Acute stress responses, corticosteroid therapy, hematological disorders, and viral infections can all produce misleading leukocyte profiles (39). Moreover, postoperative WBC count is often transiently elevated due to surgical trauma, complicating the interpretation during the early recovery phase (40). Consequently, while WBC count may contribute to the broader clinical picture, particularly in septicemia-associated PJIs (41), it is generally considered insufficient as an isolated diagnostic indicator and is best used in conjunction with more specific inflammatory biomarker (34).

Novel or less common serum biomarkers

Interleukin-6

Interleukin-6 is a pro-inflammatory cytokine produced by macrophages, synovial cells, and other immune-active tissues in response to infection or tissue injury (42). Unlike many conventional markers, IL-6 rises very rapidly—often within a few hours—following bacterial challenge, making it an attractive candidate for early detection of PJI (38). Its short half-life allows for dynamic assessment of inflammatory activity, with levels returning toward baseline quickly after the resolution of infection (43). Diagnostic thresholds for IL-6 vary between studies but often fall within single-digit pg/mL ranges, depending

on assay methodology (5). Evidence suggests that IL-6 may outperform CRP and ESR in identifying acute PJI, particularly in the immediate postoperative period when traditional markers remain elevated due to surgical trauma (44).

Despite promising diagnostic capabilities, routine IL-6 testing has been slow to enter standard PJI workups due to assay availability, cost considerations, and variability in laboratory standardization (45). Moreover, IL-6 can be transiently elevated in a range of non-infectious inflammatory states, potentially affecting specificity (40). Clinical utility is maximized when IL-6 is interpreted in conjunction with synovial fluid analysis or microbiological culture, particularly in equivocal cases (26). As point-of-care and rapid immunoassays continue to advance, IL-6 measurement may become more accessible, potentially serving as a cornerstone early-phase biomarker in PJI diagnostics (43) (Figure 1).

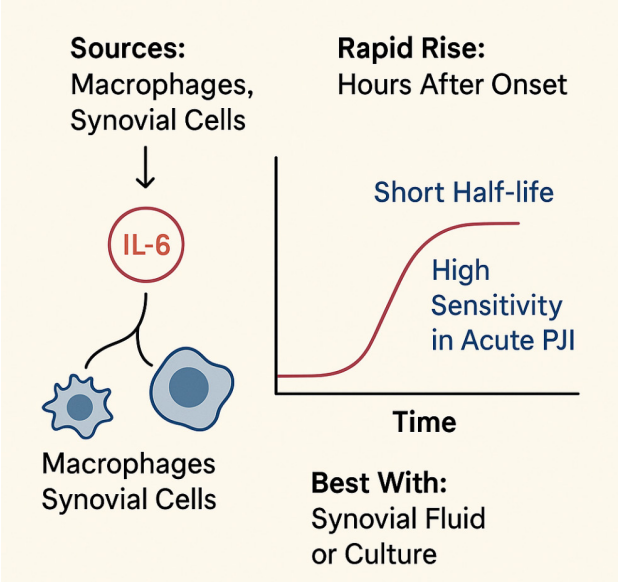

Figure 1. IL-6 dynamics and clinical utility in early diagnosis of PJI.

Procalcitonin

PCT is the prohormone of calcitonin and is increasingly recognized as a systemic marker of bacterial infection (45). Produced predominantly in extrathyroidal tissues during systemic bacterial inflammation, its release is triggered by endotoxin exposure and mediated by inflammatory cytokines (46). In bloodstream infections and sepsis, PCT levels correlate closely with bacterial load, making it a valuable sepsis biomarker (47). In the context of PJI, however, its kinetics and thresholds are less well defined (16). Several studies suggest that even modest elevations—well below the levels seen in septicemia—may hold diagnostic value in acute PJI, with reported sensitivity ranging from moderate to high in such settings (48).

One of PCT's strengths lies in its generally low elevation in viral or non-infectious inflammatory conditions, improving specificity over other serum inflammatory markers (15). This characteristic may help in differentiating postoperative inflammation from active bacterial infection. However, chronic PJIs and low-virulence organisms often fail to elicit a strong PCT response, limiting its role as a universal screening tool (49). False positives can occur in severe trauma, major surgery, or renal impairment, necessitating careful clinical interpretation (33). Overall, PCT appears most beneficial in identifying systemic infection or guiding differentiation between high-grade and low-grade PJI, particularly when combined with CRP or IL-6 measurements (50).

Serum D-dimer

D-dimer is a fibrin degradation product traditionally used in the diagnosis of thromboembolic events (25). Its relevance in PJI stems from the shared pathophysiological link between infection, coagulation activation, and fibrinolysis (39). Elevated D-dimer levels have been reported in both acute and chronic PJIs (51), with several investigations suggesting superior diagnostic accuracy compared to ESR and CRP in certain contexts (36). Unlike these traditional inflammatory markers, D-dimer elevation may reflect both systemic and local intravascular coagulation processes triggered by infection-related inflammation (52).

Nevertheless, D-dimer measurement has notable limitations, particularly its low specificity (30). Numerous conditions—including recent surgery, trauma, advanced age, malignancy, and disseminated intravascular coagulation—can independently elevate D-dimer, complicating interpretation in postoperative orthopedic patients (40). Furthermore, assay methodology and cut-off selection vary widely among studies, contributing to inconsistent sensitivity and specificity reports (53). As such, while D-dimer shows potential as an adjunctive diagnostic biomarker for PJI, its optimal use may be in conjunction with other serological and synovial biomarkers rather than as a primary screening test (51).

Presepsin

Presepsin, also known as soluble CD14 subtype (sCD14-ST), is a fragment of the monocyte surface receptor CD14 that is released during bacterial phagocytosis (41). It has gained prominence as an early and sensitive biomarker for sepsis, with levels that rise rapidly within hours of systemic bacterial infection (26). In the PJI context, emerging evidence indicates that presepsin may differentiate infectious from aseptic prosthetic failures more accurately than conventional serum markers, particularly in early or ambiguous clinical presentations (35). Unlike CRP or ESR, presepsin kinetics are not significantly influenced by surgical trauma alone, which may improve early postoperative diagnostic accuracy (47). However, the incorporation of presepsin into orthopaedic infection diagnostics remains in its infancy (54). Limited study populations, narrow assay availability, and

relatively high testing costs have restricted widespread implementation (55). Moreover, renal dysfunction can elevate presepsin levels independently of infection, necessitating careful patient selection and interpretation (1). Future large-scale, multicenter trials are required to validate cut-off values specific to PJI and to determine whether rapid presepsin testing can be effectively integrated into routine perioperative infection screening protocols (31).

TNF-alpha, IL-1β, and other cytokines

TNF-α and IL-1β are central mediators in the innate immune response, participating in the early stages of host defense against microbial invasion (33). Secreted primarily by activated macrophages and monocytes, these cytokines amplify the inflammatory cascade by recruiting immune cells to the site of infection (18), increasing vascular permeability, and upregulating the synthesis of other acute-phase proteins (56). In PJI, both TNF-α and IL-1β are frequently detected at elevated levels in serum and synovial fluid, sometimes even before traditional markers reach diagnostic thresholds (57). This early rise highlights their potential utility in catching rapidly developing infections and in differentiating infectious from aseptic prosthetic failure (31) (Figure 2).

However, the clinical applicability of TNF-α and IL-1β as routine serum biomarkers for PJI remains limited (58). Both are highly pleiotropic and can be elevated in autoimmune diseases, post-traumatic inflammation, or even systemic inflammatory response syndrome unrelated to infection (59). Moreover, their short half-life and susceptibility to rapid fluctuation make consistent detection challenging, especially in patients whose infections follow a low-grade or indolent course (31). While promising in research settings—particularly when combined with panels of multiple cytokines—these markers require further validation in standardized, large-scale diagnostic protocols before they can be integrated into clinical guidelines for PJI (60).

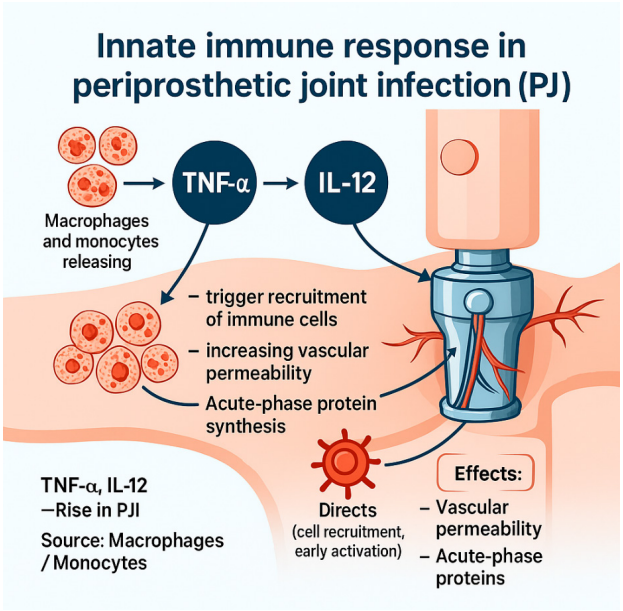

Figure 2. Early elevation of TNF-α and il 1β in PJI: central roles in innate immune activation.

Comparative findings against conventional markers.

Comparative analyses of novel serum biomarkers against established indicators such as CRP, ESR, and WBC count have revealed a complex diagnostic landscape (44). Several studies suggest that biomarkers like IL-6 and D-dimer can demonstrate equal or superior sensitivity in the acute postoperative period, where CRP and ESR are less reliable due to residual surgical inflammation (22). Similarly, cytokine panels incorporating TNF-α, IL-1β, or presepsin have shown the potential to capture early PJI cases that conventional markers may miss, especially those caused by low-virulence pathogens or presenting with minimal systemic response (33).

Nonetheless, these advantages are tempered by variability in assay standardization, cut-off thresholds, and patient population characteristics across studies (22). Conventional markers remain appealing for their wide availability, cost-effectiveness, and established interpretation frameworks (57), whereas emerging biomarkers often require specialized laboratory processing and incur higher costs (8). The consensus from current literature is that no single serum marker—novel or conventional—offers sufficient diagnostic accuracy in isolation (56). Instead, multimodal algorithms combining both established and emerging markers (44), along with synovial fluid analysis and imaging, appear to yield the highest diagnostic reliability for timely and accurate PJI detection (22).

Diagnostic accuracy (sensitivity and specificity)

Peer-reviewed studies, meta-analyses, and randomized controlled trials (RCTs) consistently demonstrate variability in the diagnostic accuracy of individual serum biomarkers for PJI (27). CRP remains the most widely studied, with pooled sensitivity typically ranging from 80% to 90% and specificity between 70% and 90%, depending on whether the setting involves acute or chronic infection (61). Meanwhile, ESR shows comparable sensitivity for chronic PJI but lower specificity, often in the 60%–80% range, largely due to non-infectious elevations. IL-6 has emerged in multiple meta-analyses as a high-performing marker, frequently reporting sensitivities above 85% and specificities exceeding 90%, particularly in early postoperative infections (57).

Novel markers such as D-dimer and presepsin have shown mixed results in systematic reviews, with some studies reporting superior sensitivity to traditional markers in select clinical contexts (6). For instance, certain RCTs indicate D-dimer sensitivities of 80%–89% and specificities of 75%–88%, while presepsin has

demonstrated sensitivities above 85% in acute bacterial PJIs (13). However, these figures often fluctuate based on population differences, cut-off values, and assay methods, underscoring the need for standardization before these markers can be universally adopted (62). The absence of large, multicenter RCTs comparing all biomarkers within the same cohort remains a critical research gap limiting definitive conclusions (55).

Value of combined biomarkers (CRP and IL-6)

Combining serum biomarkers has been shown to improve diagnostic accuracy beyond the performance of any single test in PJI (32). Multiple cohort studies report that the combination of CRP and IL-6 yields sensitivities approaching or exceeding 95% and specificities of 90%–95%, particularly in distinguishing acute infection from sterile inflammation (32). The rationale for this improvement lies in the complementary kinetics of the markers: CRP rises and remains elevated for several days post-surgery, while IL-6 peaks rapidly and declines sooner, allowing for a more precise distinction between normal postoperative responses and early infectious processes (29, 42). Similar gains in performance have been observed when D-dimer is combined with CRP, as these markers reflect both inflammatory and coagulation pathways triggered by infection (63).

Meta-analytic evidence further supports the diagnostic value of multi-marker algorithms, showing pooled positive likelihood ratios significantly higher for combined markers than for single assays (54). For example, ESR and CRP together yield sensitivities and specificities both in the 85%–95% range, which is superior to either assay alone (64). While logistic regression and machine-learning-based approaches incorporating panels of two or more biomarkers are still in experimental phases, early results suggest that these strategies may meaningfully reduce false-positive and false-negative rates, particularly in borderline or low-grade PJI cases (27,37). Adopting such combinations into clinical guidelines could represent a significant advance in timely and accurate infection detection (65).

Biomarker profiles in different PJI types

Acute postoperative PJI is characterized by a pronounced systemic inflammatory response, often occurring within the first several weeks after surgery (62). In such cases, serum biomarkers such as CRP, ESR, and IL-6 are typically elevated to marked levels, often exceeding conventional diagnostic thresholds (20). IL-6, in particular, demonstrates rapid kinetics, with rises detectable within hours of infection onset, offering a potential advantage in early diagnosis when clinical signs remain equivocal (66). Conversely, CRP concentrations usually peak within two to three days postoperatively and decline thereafter; a persistent or rising trend beyond the expected postoperative trajectory is frequently indicative of acute infection (23).

Late chronic PJI, which can manifest months or years after implantation, typically elicits a more subdued systemic inflammatory profile (36). CRP and ESR values may be only mildly elevated, and IL-6 levels often fail to reach thresholds common in acute presentations (31). The pathophysiology in chronic PJI—often involving mature bacterial biofilms—results in low-grade but persistent inflammation that may not trigger robust systemic biomarker responses (8). As a result, reliance solely on serum markers can lead to under-diagnosis, and adjunctive tests, including synovial fluid analysis and microbiological culture, become essential in guiding clinical decision-making for these delayed infections (64).

Low-grade infections

Low-grade PJIs, frequently linked to low-virulence organisms including skin commensals and coagulase-negative staphylococci, often present diagnostic difficulties because of their indolent inflammatory signature (34). These pathogens typically form dense biofilms and provoke minimal systemic immune activation (56). As a consequence, serum markers such as CRP, ESR, and white blood cell counts may remain within normal reference ranges or display only marginal elevations (5). Several studies have documented CRP levels less than 10 mg/L and ESR values under 30 mm/h in such cases, highlighting the risk of false-negative results when relying on conventional thresholds (66).

The subdued laboratory presentation of these infections demands heightened clinical suspicion, particularly when unexplained joint pain, mechanical loosening, or subtle radiographic changes are present (57). In this context, more sensitive or specific markers—such as IL-6, presepsin, or multiplex cytokine panels—may provide incremental diagnostic value (16). However, even these advanced tools may yield borderline results in low-grade PJI (14), emphasizing the importance of integrating serum biomarker data with synovial fluid analyses, intraoperative cultures, and histopathological examination (48). Early recognition of these atypical biomarker profiles is essential to prevent delayed diagnosis, prolonged morbidity, and the potential need for more extensive revision procedures (54).

Confounding factors and limitations

The diagnostic interpretation of serum inflammatory biomarkers in PJI is constrained by multiple confounding factors that can alter their baseline or dynamic levels independent of prosthetic infection (50). Comorbidities such as rheumatoid arthritis, systemic lupus erythematosus, chronic kidney disease, concurrent infections, and active malignancies can induce sustained elevations in CRP, ESR, or cytokines, while certain immunosuppressive treatments may blunt their rise even in the presence of infection (46,67). Demographic variables further influence biomarker profiles, with ESR typically increasing

with age—particularly in females—and hormonal, metabolic, or body composition differences modulating inflammatory responses (13,53). Furthermore, recent surgical procedures can transiently elevate CRP and IL-6 as part of normal postoperative healing, risking false positives if measured prematurely (2). These overlapping influences underscore the necessity of interpreting biomarker data within a comprehensive clinical context that integrates patient history (13), postoperative timing, imaging, and microbiological results, rather than relying on isolated laboratory values for definitive diagnosis (68).

Comparison with other diagnostic modalities

Compared with joint-specific investigations such as synovial fluid alpha-defensin and leukocyte esterase assays, serum inflammatory biomarkers generally offer lower (65), specificity and in some contexts, reduced sensitivity for detecting PJI, particularly in chronic or low-grade cases (62). Synovial fluid tests directly reflect the local immune response at the prosthesis–tissue interface and are less influenced by systemic comorbidities (36), thereby providing greater diagnostic certainty in equivocal presentations (42). Nonetheless, serum markers such as CRP and ESR remain integral components of internationally accepted diagnostic algorithms—including those of the Musculoskeletal Infection Society (MSIS) and the International Consensus Meeting (ICM)—where they are designated as minor criteria and serve as first-line screening tools (7,53). Within this tiered framework, serum biomarkers guide initial suspicion and patient triage, while confirmatory synovial analyses contribute greater diagnostic weight to establishing a "definite PJI" classification (53).

Discussion

This review highlights the complex interplay between host immune mechanisms and the diagnostic potential of serum inflammatory biomarkers in PJI. The pathophysiological underpinnings demonstrate that prosthetic colonization by pathogenic bacteria triggers a rapid innate immune response, characterized by activation of pattern recognition receptors, release of pro-inflammatory cytokines, and induction of acute-phase proteins (9). These cascades drive measurable changes in systemic biomarkers, yet the magnitude and temporal profile of these changes vary significantly between acute and chronic infections, influencing diagnostic reliability (58). Acute PJIs provoke robust systemic responses with marked elevations in CRP, IL-6, and related markers, whereas chronic infections, particularly those associated with mature biofilms, exhibit attenuated biomarker elevations that may fall below conventional thresholds (19,69).

Among commonly employed markers, CRP remains the most established due to its rapid synthesis following inflammatory stimuli, peaking within 48–72 hours and declining with a half-life of approximately 19 hours (49). Its diagnostic value is supported by sensitivities approaching 90% in acute PJI; however, specificity is tempered by non-infectious conditions such as autoimmune disease, malignancy, or recent surgery (9). Additionally, ESR holds complementary value, particularly in subacute or chronic settings, but is slow to normalize and is influenced by demographic and comorbid variables (29). Similarly, WBC count shows limited utility given its low sensitivity for PJI, although it may aid in detecting concomitant systemic infections (70).

Novel biomarkers such as IL-6, PCT, serum D-dimer, and presepsin offer alternative diagnostic pathways (33). However, IL-6 demonstrates superior early detection potential owing to its rapid surge within hours of infection onset and high specificity in discriminating infection from postoperative inflammation. Accordingly, PCT, with minimal elevation in viral or aseptic inflammation, shows promise in acute bacterial PJI but lacks sensitivity in chronic forms (13,30). D-dimer, reflecting fibrinolytic activity, has shown moderate to high diagnostic accuracy in several studies, though its specificity is limited by comorbid pro-coagulant states (48). Presepsin and multiplex cytokine profiling may further refine diagnostic strategies, particularly for low-grade infections where standard markers remain near baseline (25).

Comparative analyses reveal that while novel markers can surpass CRP and ESR in certain contexts, no single serum biomarker consistently achieves optimal sensitivity and specificity across all PJI subtypes (10, 67). The highest diagnostic performance is observed when markers are combined—such as CRP with IL-6—yielding synergistic gains in both sensitivity and specificity, sometimes exceeding 95% in acute settings (32,57). These multimarker approaches are especially valuable given the heterogeneous inflammatory profiles seen in acute postoperative, late chronic, and low-grade infections (71).

Type-specific differences underscore the need for tailored diagnostic interpretation (17). Acute PJIs typically show marked systemic responses that are readily captured by standard biomarkers, whereas late chronic infections produce muted signals, often requiring adjunctive synovial fluid analyses (34). Low-grade infections caused by *C. acnes* exemplify the limitations of relying solely on serum measures, as CRP and ESR may remain normal despite persistent infection (44). In such cases, synovial alpha-defensin or leukocyte esterase testing offers superior local sensitivity, justifying their prioritization within the MSIS and ICM diagnostic criteria (46).

Finally, the interpretation of serum biomarkers must account for confounders including rheumatologic disease, active malignancy, systemic infections, demographic influences, and recent surgical intervention (15). These factors can both elevate and suppress biomarker levels, leading to misclassification if considered in isolation (23,54). Integrating serum results with comprehensive clinical assessment, imaging, and targeted synovial

diagnostics reduces the risk of false positives and negatives, aligning diagnostic practice with evidence-based algorithms (45,65). The future of PJI diagnosis likely lies in precision-based, multimodal approaches that combine standardized biomarker panels with advanced analytical techniques to improve early detection and guide timely intervention (6).

Conclusion

Serum inflammatory biomarkers continue to play a central role in the diagnostic evaluation of PJI, providing prompt, accessible, and relatively low-cost indicators of systemic inflammatory activity. Established markers such as CRP and ESR remain reliable first-line tests—particularly in acute infection—while emerging biomarkers, including IL-6, PCT, D-dimer, and presepsin, offer added diagnostic value in specific scenarios and may help uncover cases that conventional tests fail to detect. Interpretation, however, must be individualized, as biomarker profiles are shaped by factors such as infection stage, microbial virulence, patient comorbidities, demographic variables, and the physiological response to recent surgery. Evidence supports a combined biomarker approach, and integrating serum assays with high-specificity synovial fluid tests, such as alpha-defensin or leukocyte esterase, enhances both sensitivity and specificity in alignment with current international criteria. Moving forward, research should focus on standardizing cut-off values, validating findings across diverse cohorts, and developing multimarker algorithms, with the ultimate goal of enabling faster, more accurate, and context-adapted PJI diagnosis.

Authors' contribution

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Software: Sina Najafi.
Supervision: Sadra Haji.
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Writing–review & editing: Sadra Haji, Alireza Aghili, Meisagh Asanjani Oskoii.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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