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REVIEW ARTICLE

Serum Calprotectin - What is the Scope of Clinical Application?

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SUMMARY

Background: **Calprotectin (CLP), a heterodimer of S100A8 and S100A9, is a calcium-binding protein with key intracellular and extracellular roles, especially in inflammatory processes. Predominantly expressed by neutrophils and monocytes, CLP is released in response to infection or inflammation and serves as a potent antimicrobial and pro-inflammatory mediator.**
Methods: **We performed a systematic search of electronic databases to identify studies evaluating serum CLP in inflammatory diseases.**
Results: **Serum CLP levels are elevated in numerous inflammatory conditions, making it a valuable biomarker for disease activity, prognosis, and therapeutic monitoring. In rheumatoid arthritis (RA), CLP reflects disease severity more accurately than conventional markers like CRP and ESR, correlates with radiographic progression, and is strongly expressed at inflammation sites. In juvenile idiopathic arthritis (JIA), serum CLP levels are significantly higher in active, treatment-naïve patients and correlate well with clinical activity. In spondyloarthritis (SpA), especially ankylosing spondylitis, CLP levels tend to be elevated, though results vary among studies. In inflammatory bowel disease (IBD), CLP is proposed as a non-invasive marker for disease burden and response to treatment. It is especially useful in systemic inflammation assessment. Elevated CLP levels are also observed in psoriasis, Behçet's disease, ANCA-associated vasculitis, and preeclampsia. CLP has emerged as a promising prognostic marker in bacterial infection and coronavirus disease 2019 (COVID-19), with higher levels correlating with ICU admission and disease severity.**
Conclusions: **Serum CLP is a promising inflammatory biomarker, though disease specificity remains limited.**
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KEYWORDS

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INTRODUCTION

Calprotectin (CLP) is a cytosolic heterodimeric protein complex composed of S100A8 and S100A9, also known as myeloid-related proteins 8 and 14 (MRP-8 and MRP-14) or calgranulin A and B [1]. Both S100A8 and S100A9 belong to the S100 family of calcium-binding proteins, which were first identified in bovine brain tissue in 1965 [2] and named "S100" for their 100% solubility in ammonium sulfate solution [3]. To

date, more than 20 S100 family members have been characterized [1,2]. S100A8/A9 expression is mainly observed in neutrophils, monocytes, and early-stage macrophages [1], and CLP is constitutively expressed in neutrophils, dendritic cells, and activated macrophages [4-6]. As a calcium-binding protein, S100 presents intracellular and extracellular functions [7]. It is secreted primarily by calcium-activated neutrophils and plays a key role as a pro-inflammatory mediator [8]. Notably, CLP expression is specifically induced during inflammation and functions as an acute-phase reactant, with serum levels significantly elevated in response to infection, trauma, and inflammatory diseases [9].

MATERIALS AND METHODS

A comprehensive literature search was conducted using electronic databases including PubMed, MEDLINE, and Embase up to May 2025. The search strategy included keywords such as “calprotectin,” “serum calprotectin,” “S100A8/A9,” “inflammatory biomarker,” “rheumatic diseases,” “autoimmune diseases,” and “infectious diseases” and specific disease terms such as “rheumatoid arthritis,” “inflammatory bowel disease,” and “COVID-19.”

Original articles, clinical studies, and relevant reviews published in English were screened for eligibility. Studies were selected based on their relevance to the clinical utility of serum calprotectin in diagnosis, disease activity monitoring, and prognostic evaluation across inflammatory, autoimmune, and infectious diseases. Articles focusing on non-serum samples (e.g. fecal or synovial fluid CLP) were included only when clinically relevant to serum CLP interpretation or mechanistic understanding.

Data extraction and synthesis were performed manually. Selected studies were critically reviewed and summarized to provide a comprehensive overview of serum CLP’s clinical implications and to compare its diagnostic and prognostic value with conventional inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT).

Antimicrobial and immunomodulatory functions of CLP

CLP is a potent antimicrobial protein complex [10]. It has been shown to exert bacteriostatic and fungistatic effects against a range of pathogens, including *Escherichia coli* and *Staphylococcus aureus* [11]. CLP limits microbial growth by sequestering essential metal ions. Within its heterodimeric structure, CLP contains six histidine residues that form high-affinity binding sites for manganese (Mn^{2+}), as well as two distinct binding sites for zinc (Zn^{2+}), leading to metal chelation-mediated microbial growth inhibition [10,12-14]. This metal starvation impairs microbial metabolism, oxidative stress response, and proliferation. In addition, CLP exhibits bacteriostatic effects against spirochetes such as *Borrelia burgdorferi* through both metal chelation and direct physical interaction that disrupts bacterial growth [15,16].

Beyond its antimicrobial action, extracellular CLP plays a key immunomodulatory role by engaging Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE) on immune and endothelial cells, thereby promoting the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [8,17]. CLP is also a major component of neutrophil extracellular traps (NETs), released during NETosis - a specialized form of neutrophil cell death that regulates immune responses at sites of inflammation [18]. CLP within NETs further amplifies inflammation through RAGE and TLR4 signaling, but excessive NET accumulation has been linked to tissue damage and chronic inflammation [18].

In the presence of calcium, CLP enhances microtubule polymerization and stabilizes the cytoskeleton by promoting tubulin filament assembly [1]. Structural changes induced by increased Ca^{2+} concentrations at infection sites significantly enhance CLP’s affinity for Mn^{2+}, Zn^{2+}, and Fe^{2+}, increasing its antimicrobial efficacy [11,14]. Studies using S100A9 knockout mice, which lack functional CLP heterodimers, demonstrate reduced granulocyte tubulin levels and diminished neutrophil infiltration into inflammatory lesions, suggesting a critical role in immune cell migration [19]. Owing to its diverse antimicrobial and immunoregulatory functions, CLP is increasingly recognized as a valuable biomarker for infection and inflammatory conditions, including rheumatic diseases [17,20].

Serum calprotectin as a proximal biomarker of neutrophil activation

CLP has emerged as a valuable proxy biomarker for neutrophil activation in biological fluids [8]. While CRP is widely used as a systemic acute-phase reactant induced by interleukin-6 (IL-6), CLP reflects localized inflammation more directly. Its expression near inflammatory foci allows it to function as a site-specific biomarker. For example, in rheumatic diseases with joint involvement, CLP levels measured in synovial fluid can indicate the degree of local inflammation. Similarly, in autoimmune vasculitis, serum CLP can serve as a diagnostic tool for evaluating vascular inflammation.

Serum CLP is well-studied as an inflammatory biomarker, with increasing clinical attention due to its stability and assay reproducibility [1,21,22]. In healthy adults, serum CLP concentrations are typically below 1 μg/mL, but levels may increase up to 100-fold during active inflammation [23]. These properties highlight CLP’s potential utility as a diagnostic and monitoring marker across a wide range of inflammatory and infectious conditions (Figure 1).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a heterogeneous autoimmune disease characterized by chronic polyarthritis,

Table 1. Clinical implication of serum calprotectin.

Entity	Rheumatic disease	Infectious disease
Diagnostic work-up	Autoimmunity evaluation	Pathogen discrimination
		Bacterial infection
		Superinfection
Inflammatory marker	Disease activity/progression	Dysregulated immune function
Predictive tool	Severity	Severity
	Therapeutic response	
	Relapse risk / Prognosis	Prognosis

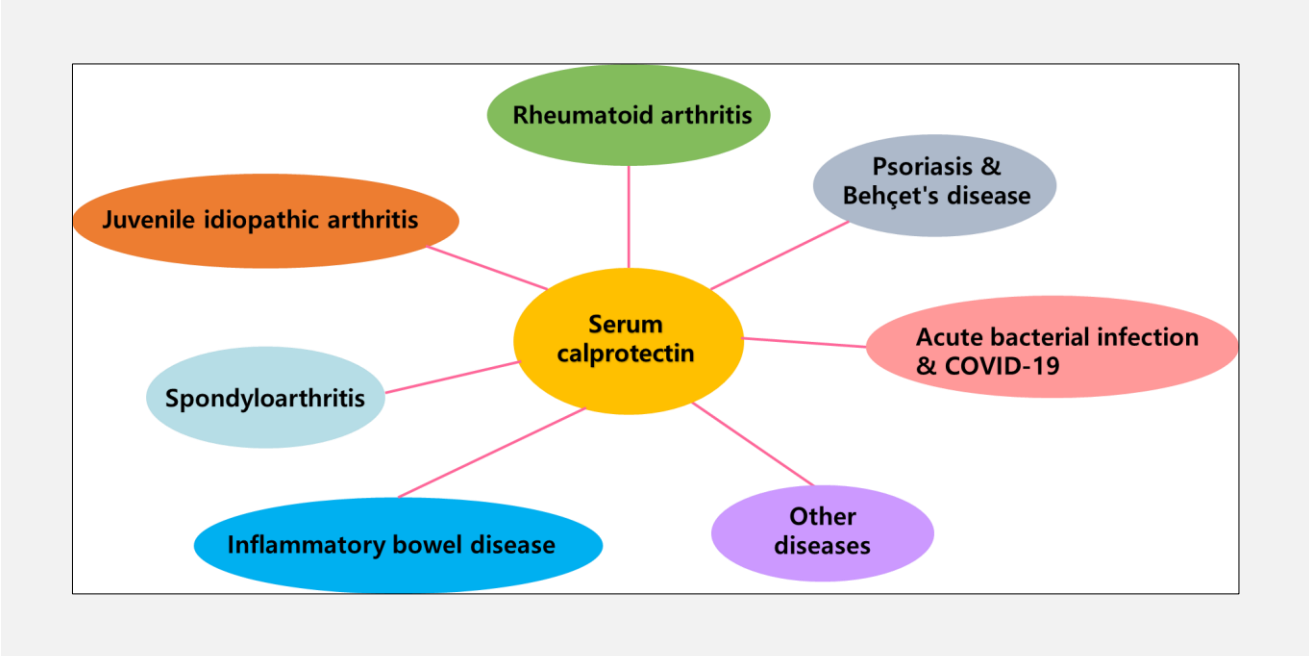

Figure 1. Serum calprotectin and various disease conditions.

COVID-19 coronavirus disease 2019.

joint destruction, functional disability, and increased mortality [3]. CLP is secreted by activated macrophages and neutrophils in inflamed joints and plays a pivotal role in RA pathogenesis by promoting chemotaxis, leukocyte adhesion, phagocyte migration, and modulation of inflammatory responses [1]. Notably, CLP expression is markedly elevated in synovial macrophages, particularly near the cartilage-pannus junction (CPJ), a key site of joint erosion [24].

Serum CLP demonstrated high diagnostic performance for RA, with a sensitivity of 88.6% and specificity of 100% at a cutoff value of 93.9 µg/dL [25]. Higher CLP levels have been associated with seropositivity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) [3,26,27]. Longitudinal studies show that CLP better reflects disease activity than conventional markers such as CRP and ESR and correlates with ultrasonographic scores like disease activity score 28 (DAS28) [3,28].

Importantly, CLP levels remain elevated in patients with subclinical inflammation even when CRP is normal [29].

CLP levels have also been associated with radiographic progression and treatment response [8]. In experimental arthritis models, CLP depletion significantly reduced cartilage destruction [7]. Serum CLP reduction following TNF-α inhibitor therapy, such as infliximab, correlated with therapeutic efficacy [30]. Furthermore, serum

CLP levels > 1,500 ng/mL during remission predicted a 68% risk of relapse within 6 months [31].

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) represents a group of chronic autoimmune arthritis in children and adolescents [32]. One major challenge in pediatric rheumatology is the identification of predictive biomarkers for disease activity, treatment response, and relapse. Serum CLP has been consistently elevated in treatment-naïve children with active JIA across all subtypes [32,33].

CLP levels show a strong correlation with disease activity scores, including juvenile arthritis disease activity score 10 (JADAS10) and DAS28, and correlate positively with CRP [33-35]. Moreover, CLP outperforms traditional inflammatory markers such as ESR and CRP in reflecting disease activity and may aid in therapeutic monitoring and relapse prediction [34,35].

Spondyloarthritis

Spondyloarthritis (SpA) encompasses a group of inflammatory arthritis including ankylosing spondylitis (AS), psoriatic arthritis, peripheral SpA, IBD-associated arthritis, and juvenile SpA [20]. CLP is strongly expressed in the synovial tissue of SpA patients [1]. Several studies report elevated serum CLP levels in SpA compared to controls, correlating with disease activity and functional status [20,36].

In AS, serum CLP levels are significantly higher than in healthy individuals and are proposed to differentiate AS from other conditions [37]. Furthermore, CLP correlates with radiographic severity and can serve as a predictor for radiological progression [8]. The decline in serum CLP after one month of treatment has been associated with achieving assessment in SpA 40 (ASAS40) therapeutic response criteria [37].

However, some studies have shown no significant difference in CLP levels between AS patients and healthy controls, indicating interstudy variability [1]. Nevertheless, CLP has demonstrated a high standardized response mean (SRM) in response to infliximab, suggesting its potential as a useful marker for treatment monitoring in both AS and psoriatic arthritis [30].

Inflammatory bowel disease

Inflammatory bowel disease (IBD), encompassing ulcerative colitis and Crohn's disease, is a chronic inflammatory disorder of the gastrointestinal tract with multifactorial etiology, involving genetic predisposition, environmental triggers, gut microbiota, and immune dysregulation [38]. Recent studies have highlighted the potential of serum CLP as a valuable biomarker for diagnosis, disease monitoring, and treatment response in IBD [38,39]. Serum CLP levels have been found to correlate with systemic inflammation and may complement fecal calprotectin in capturing broader inflammatory activity [39].

Given the rising global prevalence of IBD, serum CLP offers a minimally invasive, accessible tool for clinicians in disease stratification, prognostication, and follow-up of patients [38,39].

Psoriasis and Behçet's disease

Psoriasis is a chronic immune-mediated skin disorder characterized by erythematous plaques with epidermal hyperproliferation, immune cell infiltration, and vascular remodeling [40]. CLP has been found to be markedly overexpressed in keratinocytes of psoriatic lesions [41]. Additionally, serum CLP levels are significantly elevated in psoriasis patients compared to healthy controls, supporting its role as a potential systemic inflammatory marker [42].

Behçet's disease is a multisystem vasculitis disorder presenting with recurrent oral and genital ulcers, uveitis, arthritis, and vascular involvement [43]. Elevated serum CLP levels have been observed in patients with Behçet's disease relative to controls, likely reflecting underlying vascular inflammation [44]. However, current evidence does not yet establish a clear association between serum CLP and disease severity in Behçet's disease [44].

Acute infection and sepsis

In acute infections, early differentiation of causative pathogens is critical for timely and appropriate management. PCT and cluster of differentiation (CD)14 subtype, known as presepsin, have been widely investigated as biomarkers due to their ability to distinguish bacterial from non-bacterial infections and guide antibiotic stewardship [45]. PCT, in particular, is more widely adopted in clinical laboratories owing to its technical feasibility.

Recent evidence suggests that serum CLP, a marker of neutrophil activation, may outperform PCT in differentiating bacterial respiratory infections from viral or mycoplasma etiologies, with an area under the receiver operating characteristic (ROC) curve (AUC) exceeding 0.8, compared to PCT's AUC of 0.5 - 0.7 [46]. These findings support the clinical utility of CLP in infection stratification and align with prior studies reporting elevated CLP levels in inflammatory conditions with neutrophil activation, including sepsis [47-49].

COVID-19 and superinfection

Coronavirus disease 2019 (COVID-19) is a systemic viral illness primarily targeting the respiratory system, but it also triggers dysregulated immune responses, cytokine storm, and multi-organ involvement [17,50]. Clinical manifestations range from mild upper respiratory symptoms to pneumonia, disseminated intravascular coagulation, respiratory failure, shock, and death. Biomarkers such as CRP, ESR, and ferritin have been widely used to assess disease severity, though their specificity remains limited.

Recent studies have shown that serum CLP levels are significantly elevated in COVID-19 patients compared to healthy controls (3,760 vs. 2,100 ng/mL), with a high diagnostic accuracy (AUC 0.842) in distinguishing

COVID-19 infection [17]. CLP levels have been associated with disease severity, rising up to 5,700 ng/mL in critically ill patients and negatively correlating with respiratory function [51,52]. Additionally, CLP concentrations are markedly higher in patients requiring intensive care and serve as a strong predictor for intensive care unit (ICU) admission, with a cutoff of 3,230 ng/mL yielding an AUC of 0.871 - surpassing CRP and PCT in predictive performance [17,50]. During convalescence, serum CLP levels tend to normalize, reflecting resolution of systemic inflammation [17].

Secondary bacterial infections, including bloodstream infections, have been reported in severe COVID-19 patients, particularly those in the ICU. In cases of vancomycin-resistant *Enterococci* (VRE) bacteremia, serum CLP levels were significantly elevated and demonstrated diagnostic utility, with a cutoff of 31.29 µg/mL yielding 60% sensitivity and 96% specificity [53]. This finding suggests a potential role for CLP in identifying superinfections in critically ill COVID-19 patients, especially when conventional biomarkers are inconclusive.

Other diseases

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a life-threatening autoimmune disease that frequently leads to rapidly progressive renal failure [54,55]. Neutrophils play a central role in the pathogenesis of endothelial injury in AAV. Serum CLP levels are significantly elevated in patients with active AAV compared to healthy controls [54,55]. Notably, elevated CLP levels have also been reported in patients in clinical remission, suggesting ongoing subclinical inflammation. Therefore, CLP has been proposed as a potential biomarker for assessing relapse risk in AAV [8].

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder involving multiple organ systems. CLP has demonstrated diagnostic value in assessing disease activity, particularly in patients with moderate to severe SLE, defined by a SLE disease activity index (SLEDAI) score ≥ 6. In one study, serum CLP showed an AUC of 0.942 with 100% sensitivity and 82.5% specificity [56]. CLP levels were positively correlated with conventional markers of disease activity, including anti-double stranded DNA antibodies and decreased complement C3 levels [56,57].

In preeclampsia, systemic inflammation, immune dysregulation, and endothelial dysfunction are considered key pathogenic mechanisms [58]. Serum CLP levels are significantly elevated in affected individuals, reflecting heightened systemic inflammatory activity [58].

CONCLUSION

Serum CLP has emerged as a promising biomarker for the diagnosis, assessment of inflammation, and prognosis of various inflammatory diseases (Table 1). Across a range of autoimmune and infectious conditions, elevated serum CLP levels consistently correlate with disease activity and may offer additional value beyond conventional inflammatory markers. Particularly in autoimmune diseases, CLP functions as an acute phase reactant and reflects ongoing immune activation. However, its limited disease specificity restricts its role as a standalone diagnostic tool. Further large-scale and disease-specific studies are warranted to establish standardized reference values and to support the integration of CLP into routine clinical practice.

Declaration of Interest:

The authors declared that there were no conflicts of interest that could influence the study.

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