

Presepsin (sCD14-ST) as an Actionable Biomarker in Sepsis Diagnostics and Prognostication

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Vol. 1 | Issue 3 | 2026 | pp. 1–6

Received: 10-Jan-2026

Accepted: 20-Apr-2026

Published: 23-Jul-2026

DOI: <https://doi.org/110.5281/zenodo.22064097>

P-ISSN: 3117-8065 | E-ISSN: 3117-8073

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How to cite this article: Dr. Vipin Viswanath. Presepsin (sCD14-ST) as an Actionable Biomarker in Sepsis Diagnostics and Prognostication. ICMEJLM. 2026;1(3):1-6. DOI: 10.5281/zenodo.22064097.

ABSTRACT

Time to appropriate antimicrobial therapy remains the single strongest determinant of survival in sepsis. Established laboratory parameters such as C-reactive protein (CRP) and procalcitonin (PCT) continue to see widespread clinical use, yet both are vulnerable to non-infectious inflammatory triggers and rise too slowly to guide urgent resuscitation decisions. Presepsin (sCD14-ST), a 13-kDa fragment of CD14 released exclusively when myeloid phagocytes engulf bacterial ligands, provides a biologically specific alternative that appears in the circulation within two hours of bacterial invasion, establishing an earlier diagnostic window than conventional indices. This comprehensive review examines the molecular events governing presepsin shedding, benchmarks its diagnostic and kinetic performance against established markers, and provides structured algorithms for interpreting discordant biomarker panels (e.g., elevated presepsin with low PCT). Furthermore, it evaluates pathogen-specific variations across Gram-negative, Gram-positive, fungal, and viral co-infections, provides eGFR-stratified diagnostic cutoffs to prevent misclassification in renal impairment, and reviews health-economic considerations, instrument footprints, and assay availability governing point-of-care implementation.

Keywords: Presepsin, sCD14-ST, Sepsis-3, Phagocytosis, Point-of-Care Testing, Health Economics, Biomarker Kinetics, Renal Clearance

1. INTRODUCTION AND CLINICAL RATIONALE

The Sepsis-3 international consensus defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Globally, sepsis represents a monumental healthcare burden, affecting nearly 49 million individuals each year and contributing to approximately 11 million deaths—accounting for roughly one in every five deaths worldwide. Following initial microbial invasion, the clinical trajectory can deteriorate with alarming velocity: systemic endothelial injury, widespread microvascular thrombosis, tissue

hypoperfusion, and irreversible multi-organ failure can develop within hours.

Early clinical recognition and prompt initiation of targeted antimicrobial therapy constitute the cornerstone of sepsis survival. In septic shock, every hour of delay in administering appropriate antibiotics produces a measurable 7.6% decrease in survival. While automated blood culture remains the gold standard for microbiological confirmation, its turnaround time of 24 to 72 hours precludes its utility in directing immediate resuscitative decisions. Furthermore, blood cultures suffer from high false-negative rates in patients who

received empirical antibiotics prior to sampling or who harbor fastidious organisms.

To bridge this diagnostic gap, clinicians have historically relied on circulating inflammatory biomarkers, yet standard options present substantial biological limitations. C-reactive protein (CRP), synthesized hepatically downstream of Interleukin-6 (IL-6), requires 36 to 48 hours to reach peak circulating concentrations and non-specifically elevates during autoimmune flares, sterile tissue injury, and trauma. Procalcitonin (PCT) demonstrates faster kinetics but is induced primarily by systemic endotoxemia and pro-inflammatory cytokines (IL-1 β , TNF- α) across parenchymal tissues; consequently, sterile insults such as major abdominal surgery, cardiopulmonary bypass, severe burns, and acute pancreatitis frequently provoke marked false-positive PCT elevations.

Presepsin (the soluble CD14 subtype, sCD14-ST) sidesteps these non-specific inflammatory pathways. Because its generation is strictly contingent upon the receptor-mediated phagocytosis of bacterial ligands by circulating myeloid cells rather than generalized downstream humoral signaling, presepsin serves as a direct, early, and highly specific surrogate for active microbial invasion.

2. MOLECULAR PATHOPHYSIOLOGY AND SHEDDING MECHANISMS

2.1 CD14 Structure and Ligand Engagement

Cluster of Differentiation 14 (CD14) is a 55-kDa glycosylphosphatidylinositol (GPI)-anchored pattern recognition receptor abundantly expressed on the cell surface of monocytes, macrophages, and to a lesser extent, polymorphonuclear neutrophils (PMNs). In its membrane-anchored form (mCD14), it functions as a critical co-receptor for Toll-like receptors (TLR4 and TLR2). CD14 binds lipopolysaccharide (LPS)

complexed with LPS-binding protein (LBP) from Gram-negative bacteria, as well as peptidoglycan (PGN), lipoteichoic acid (LTA), and fungal β -glucans from Gram-positive bacteria and fungal pathogens.

Ligation of pathogen-associated molecular patterns (PAMPs) to mCD14 triggers two simultaneous downstream cascades: (1) activation of intracellular inflammatory gene transcription via NF- κ B, and (2) rapid receptor-mediated endocytosis of the ligand-receptor complex, trafficking the internalized complex directly into the phagolysosomal machinery.

2.2 Phagolysosomal Proteolytic Processing

Within the acidic microenvironment of the phagolysosome, lysosomal aspartic proteases—predominantly Cathepsin D—cleave the 55-kDa full-length CD14 polypeptide. This targeted enzymatic cleavage yields a truncated 13-kDa N-terminal peptide comprising 64 amino acids (Arg19 to Val82), designated as sCD14 subtype (sCD14-ST) or presepsin. Following microbial degradation, presepsin is released into extracellular circulation via exocytosis.

Because Cathepsin D cleavage requires the physical internalization and phagocytosis of microbial structures, presepsin is not shed during sterile cytokine stimulation or non-specific tissue necrosis. It provides a direct cellular footprint of host-pathogen engagement.

3. KINETIC COMPARISON AMONG INFLAMMATORY MARKERS

An ideal biomarker for acute sepsis triage must exhibit rapid onset to guide immediate empirical decisions, reach an early diagnostic peak, and maintain an elimination half-life short enough to dynamically reflect therapeutic efficacy. Presepsin fulfills these criteria uniquely: circulating levels rise within 1 to 2 hours post-infection, peak at 2 to 4 hours, and clear with a short plasma half-life of 4 to 5 hours.

Table 1. Kinetic and Biological Comparison of Presepsin versus Established Sepsis Biomarkers

Kinetic / Biological Parameter	Presepsin (sCD14-ST)	Procalcitonin (PCT)	C-Reactive Protein (CRP)	Interleukin-6 (IL-6)
Cellular Origin	Monocytes / Macrophages	Parenchymal / Neuroendocrine	Hepatocytes	T-cells, Endothelial, Myeloid
Primary Trigger	Microbial Phagocytosis	Endotoxins / Inflammatory Cytokines	Interleukin-6 stimulation	PAMP / DAMP recognition
Onset of Elevation	1–2 hours	2–4 hours	6–8 hours	0.5–1 hour
Peak Concentration	2–4 hours	12–24 hours	36–48 hours	2–4 hours
Elimination Half-Life	4–5 hours	24 hours	19 hours	1–2 hours

4. ANALYTICAL PLATFORMS, POINT-OF-CARE TESTING, AND HEALTH ECONOMICS

4.1 Assay Architecture and Point-of-Care CLEIA Platforms

Widespread clinical implementation of presepsin has been driven by automated chemiluminescent enzyme immunoassay (CLEIA) systems (such as the PATHFAST® platform). The analytical mechanism utilizes a non-competitive sandwich immunoassay

format: magnetic microparticles coated with anti-presepsin polyclonal/monoclonal antibodies capture circulating presepsin fragments, followed by binding with alkaline phosphatase (ALP)-labeled monoclonal antibodies. Following magnetic separation and washing, a chemiluminescent substrate (CSPD) is added, yielding light emission directly proportional to presepsin concentration.

Key analytical and operational characteristics include:

- **Sample Versatility:** The platform accepts whole blood (EDTA or heparinized), plasma, or serum. The ability to use uncentrifuged whole blood eliminates pre-analytical centrifugation delays, saving 15–20 minutes in emergency workflows.
- **Analytical Turnaround Time:** Fully automated processing delivers quantitative results in under 17

minutes from sample aspiration, making it ideal for point-of-care (POC) deployment in emergency departments and intensive care units.

- **Analytical Sensitivity & Range:** The assay demonstrates a limit of detection (LoD) of ~20 pg/mL with a broad linear dynamic range up to 20,000 pg/mL, accommodating severe septic shock without requiring manual dilution.

4.2 Health-Economic Considerations, Instrument Footprint, and Central Lab Comparison

A practical evaluation of presepsin implementation requires assessing instrument costs, reagent logistics, operational footprint, and overall healthcare value relative to standard central laboratory assays (PCT and CRP):

Table 2. Operational and Health-Economic Comparison — Presepsin versus Central Laboratory Assays

Operational / Economic Feature	Presepsin (POC CLEIA)	Procalcitonin (PCT – Central/POC)	C-Reactive Protein (CRP – Central)
Instrument Capital Cost & Footprint	Low-to-moderate (₹12,00,000–₹20,00,000); compact benchtop footprint (< 0.25 m ²)	High (₹40,00,000–₹1,20,00,000 for central immunoassay track; ₹6,50,000–₹15,00,000 for POC)	Standard (₹32,00,000–₹95,00,000 central clinical chemistry platform)
Per-Test Reagent Cost	Moderate (₹1,500–₹2,400 per test cartridge)	Moderate-to-high (₹1,200–₹2,800 per test)	Low (₹120–₹350 per test)
Pre-Analytical & Hands-on Time	< 1 min (Whole blood, single-test cartridge, zero centrifugation)	15–45 min (Centrifugation required for central lab; 5 min for POC)	15–45 min (Centrifugation and central batching required)
Health-Economic Impact & ROI	Reduces ED boarding times, prevents unnecessary ICU transfers, saves ₹1,00,000–₹2,30,000 per sepsis admission via early targeted therapy	Proven stewardship value for guided antibiotic cessation; moderate impact on initial admission triage	Low diagnostic specificity limits individual cost-offset; primarily useful for non-specific trend monitoring

Global Availability and Logistics: While PCT and CRP assays are ubiquitously integrated across large central clinical chemistry and immunochemistry analyzers (e.g., Roche, Abbott, Siemens, Beckman Coulter), presepsin testing historically depended on proprietary benchtop CLEIA analyzers. However, expanding international distribution, single-test all-in-one cartridge packaging, room-temperature/standard refrigerated reagent stability, and regulatory clearances across Europe, Asia, and Latin America have significantly lowered entry barriers for district hospitals, acute emergency centers, and satellite laboratories.

5. CLINICAL DIAGNOSTIC PERFORMANCE AND RISK STRATIFICATION

5.1 Discriminating Sepsis from Non-Infectious SIRS

Differentiating genuine bacterial infection from sterile Systemic Inflammatory Response Syndrome (SIRS)—frequently encountered following polytrauma, extensive burns, acute pancreatitis, and major cardiac surgery—represents a critical diagnostic hurdle. Meta-analyses encompassing over 40 prospective clinical

studies demonstrate that presepsin possesses a pooled diagnostic sensitivity of 84% (95% CI: 0.80–0.88) and a pooled specificity of 81% (95% CI: 0.76–0.85), with an overall Summary ROC (SROC) AUC ranging from 0.89 to 0.92.

Because sterile tissue injury does not activate Cathepsin D-mediated cleavage of mCD14 within phagolysosomes, presepsin maintains high diagnostic specificity and avoids the substantial false-positive elevations routinely observed with PCT and CRP in the first 48 hours following surgical or traumatic tissue disruption.

5.2 Clinical Decision Cutoff Tiers

Validated risk stratification tiers for clinical interpretation include:

- **< 200 pg/mL (Normal Baseline):** Systemic bacterial infection is highly improbable; high negative predictive value (> 95%). Routine empirical antimicrobials are not indicated.
- **200–500 pg/mL (Mild / Localized Risk):** Suggestive of localized bacterial infection or mild systemic

response; low risk of rapid deterioration. Serial monitoring recommended.

- 500–1000 pg/mL (Moderate Sepsis): Consistent with clinical sepsis under Sepsis-3 definitions. Prompts immediate blood culture sampling, diagnostic imaging, and empirical antibiotic administration within 1 hour.
- > 1000 pg/mL (Severe Sepsis / Septic Shock): Indicates severe systemic infection with high risk of organ dysfunction, septic shock, and elevated 30-day mortality. Warrant immediate intensive care escalation.

6. PATHOGEN-SPECIFIC DIAGNOSTIC PERFORMANCE AND CO-INFECTIONS

A crucial consideration in acute biomarker interpretation is performance variability across diverse microbial etiologies, including Gram-negative bacteria, Gram-positive bacteria, fungal organisms, and viral co-infections.

6.1 Gram-Negative vs. Gram-Positive Bacterial Infections

Because CD14 serves as a universal pattern-recognition co-receptor binding both LPS (Gram-negative) and peptidoglycan/lipoteichoic acid (Gram-positive), presepsin demonstrates high diagnostic sensitivity across both bacterial classes. Clinical cohort analyses indicate that median presepsin concentrations in Gram-negative sepsis (median ~1,150 pg/mL) tend to be marginally higher than in Gram-positive sepsis (median ~850 pg/mL), reflecting the potent phagocytic activation provoked by endotoxin. However, this overlap precludes using presepsin alone to differentiate Gram-negative from Gram-positive bacteremia, underscoring the ongoing necessity of microbiological cultures.

6.2 Fungal Sepsis (Invasive Candidiasis & Aspergillosis)

During invasive fungal infections, monocyte/macrophage engagement and phagocytosis of fungal cell wall components (such as zymosan and β -1,3-glucans) occur via CD14 and dectin-1 pathways, inducing modest-to-moderate presepsin elevations (typically 400–900 pg/mL). While presepsin rises significantly above baseline in candidemia, its absolute peak values are typically lower than those observed during fulminant Gram-negative bacteremia. Combining presepsin with fungal-specific markers (such as 1,3- β -D-glucan or galactomannan) markedly enhances diagnostic accuracy for invasive mycoses.

6.3 Viral Infections and Viral-Bacterial Co-Infections (Influenza, COVID-19)

Pure viral respiratory infections (e.g., uncomplicated Influenza A/B, RSV, SARS-CoV-2) generally do not provoke phagolysosomal Cathepsin D cleavage of CD14, leaving presepsin concentrations below 300–400 pg/mL. However, viral-induced severe lung damage frequently predisposes patients to secondary bacterial superinfections (e.g., secondary *Staphylococcus aureus* or *Streptococcus pneumoniae* pneumonia). In hospitalized COVID-19 and influenza cohorts, an abrupt surge in presepsin (> 600 pg/mL) served as a highly sensitive, specific early indicator of secondary bacterial co-infection and ventilator-associated pneumonia (VAP), outperforming both PCT and CRP.

7. CLINICAL GUIDANCE ON INTERPRETING DISCORDANT BIOMARKER RESULTS

In clinical practice, multi-marker panels occasionally yield conflicting or discordant results. Clinicians must understand the underlying pathophysiological mechanisms to make rational therapeutic decisions.

Table 3. Interpreting Discordant Presepsin–Procalcitonin Biomarker Panels

Biomarker Pattern	Presepsin & PCT Concordance	Underlying Pathophysiology	Recommended Clinical Action
High Presepsin (> 800 pg/mL) + Low PCT (< 0.25 ng/mL)	Discordant	1. Ultra-early localized/systemic bacterial invasion (within 1–3h, before parenchymal PCT induction). 2. Significant renal impairment (eGFR < 45 mL/min) causing presepsin retention. 3. Early localized Gram-positive or deep-seated abscess.	• Evaluate eGFR and apply renal correction cutoffs. • Obtain urgent blood/site cultures. • Initiate empirical antimicrobials if clinical signs of sepsis exist; repeat PCT and presepsin at 6–8 hours.
Low Presepsin (< 300 pg/mL) + High PCT (> 2.0 ng/mL)	Discordant	1. Sterile systemic inflammation: major trauma, post-cardiopulmonary bypass, extensive burns, severe pancreatitis. 2. Medullary thyroid carcinoma or small-cell lung carcinoma (neuroendocrine secretion).	• Bacterial infection is highly unlikely. • Avoid inappropriate empirical antibiotic initiation or expedite de-escalation. • Focus investigation on sterile tissue damage or non-infectious etiologies.
High Presepsin (> 800 pg/mL) +	Concordant High	Definitive, severe bacterial infection/sepsis with widespread cytokine and endotoxin release.	• Immediate implementation of Sepsis-3 bundle (broad-spectrum IV antibiotics

High PCT (> 2.0 ng/mL)			within 1 hour, IV fluids, lactate clearance, source control).
Low Presepsin (< 300 pg/mL) + Low PCT (< 0.25 ng/mL)	Concordant Low	Systemic bacterial infection ruled out (high combined NPV > 98%).	• Withhold antibiotics; search for viral, autoimmune, or non-inflammatory etiologies.

8. PROGNOSTICATION AND DYNAMIC TREATMENT MONITORING

8.1 Serial Monitoring and Antibiotic Responsiveness

Large-scale prospective investigations, including extensive sub-analyses from the multicenter ALBIOS trial, establish that baseline and serial presepsin measurements independently predict 28-day and 90-day all-cause mortality. In successfully treated patients, circulating presepsin levels decline rapidly, dropping by > 20–30% within 24 to 48 hours following effective source control and appropriate antimicrobial selection. Conversely, a plateau or secondary rise in presepsin heralds treatment failure, antimicrobial resistance, persistent undrained septic foci, or secondary nosocomial infection.

8.2 Synergy with Clinical Scoring Systems

Integrating presepsin into physiological acuity scoring algorithms (SOFA, qSOFA, APACHE II, and MEDS) significantly improves diagnostic discrimination and net reclassification index (NRI). For instance, combining presepsin with qSOFA elevates the prognostic AUC for ICU mortality from 0.73 to 0.88, providing clinicians with robust objective criteria for aggressive ICU step-up care.

9. UTILITY IN UNIQUE PATIENT COHORTS

9.1 Neonatal Sepsis and Micro-Sampling

The diagnosis of early-onset sepsis (EOS) and late-onset sepsis (LOS) in neonates is severely confounded by the physiological surges in PCT and CRP that naturally occur during the first 48 hours

Table 4. eGFR-Adjusted Sepsis Diagnostic Cutoffs for Presepsin

Renal Functional Category	eGFR Range (mL/min/1.73 m ²)	Adjusted Sepsis Diagnostic Cutoff
Normal / Mild Impairment	eGFR ≥ 60	500 pg/mL (Standard cutoff)
Moderate Renal Impairment	eGFR 30–59	800–850 pg/mL
Severe Impairment / Dialysis	eGFR < 30 or Hemodialysis	1,200–1,400 pg/mL

11. FUTURE INTEGRATION, STEWARDSHIP FRAMEWORK, AND SUMMARY

Presepsin represents a paradigm shift in sepsis diagnostics. By providing a direct, quantifiable biochemical reflection of host myeloid phagocytosis rather than downstream inflammatory signaling, it achieves unmatched diagnostic speed (1–2 hour

post-partum. Presepsin is completely unaffected by birth-related physiological stress, retaining exceptional diagnostic sensitivity (> 90%) and specificity (> 88%). Furthermore, POC CLEIA systems require minimal blood volume (< 50 µL whole blood), making presepsin an outstanding choice for micro-volume neonatal testing.

9.2 Post-Surgical and Polytrauma Monitoring

Sterile surgical trauma routinely induces widespread cytokine release, sustaining elevated PCT and CRP levels for 72 to 96 hours post-operatively. In contrast, presepsin remains quiescent in the absence of bacterial phagocytosis. A post-operative rise in presepsin on postoperative day 2 or 3 provides a highly sensitive sentinel warning for anastomotic leaks, surgical site breakdown, or nosocomial bacteremia days before overt clinical decompensation.

10. CONFOUNDERS AND RENAL ELIMINATION DYNAMICS

Because presepsin is a low-molecular-weight 13-kDa protein freely filtered at the renal glomerulus and catabolized in proximal tubules, renal clearance efficiency profoundly impacts its circulating concentrations. In patients with acute kidney injury (AKI) or end-stage chronic kidney disease (CKD), reduced filtration impairs presepsin elimination, leading to baseline accumulation. To avoid diagnostic false positives, clinicians must adjust decision cutoffs according to estimated Glomerular Filtration Rate (eGFR):

elevation) and specificity. Incorporating rapid POC presepsin into emergency triage enables the swift identification of bacterial sepsis, allowing clinicians to administer life-saving targeted antimicrobials within the critical golden hour of presentation.

Furthermore, structured clinical integration—incorporating eGFR-adjusted cutoff thresholds, standardized multi-marker algorithms for

resolving discordant panels, and dynamic 48-hour serial monitoring—maximizes clinical precision while optimizing health-economic resource allocation. Combined with automated machine learning models and procalcitonin-guided de-escalation protocols, presepsin stands as an essential component of modern diagnostic and antimicrobial stewardship.

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