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Original Research

The Role of Biomarkers in Infectious Disease Diagnosis: A Comparative Study of C-Reactive Protein, Procalcitonin and Presepsin.

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Abstract

Background: Rapid and accurate diagnosis of infection–and its differentiation from non-infectious inflammation and from viral illness–remains a major clinical challenge. Culture-based methods are definitive but slow, prompting interest in host-response biomarkers that can support early decision-making and antibiotic stewardship. *Objectives:* To evaluate and compare the diagnostic performance of three widely used host-response biomarkers–C-reactive protein (CRP), procalcitonin (PCT), and presepsin–for the diagnosis of bacterial infection and sepsis, using microbiological culture and clinical adjudication as reference standards. *Methods:* In this prospective, observational, cross-sectional study conducted at a tertiary care centre, adult patients with suspected infection had CRP, PCT, and presepsin measured at presentation. Patients were classified as having bacterial infection, viral/non-bacterial illness, or non-infectious systemic inflammation on the basis of cultures and clinical adjudication. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) analysis, with sensitivity, specificity, and area under the curve (AUC) calculated at optimal cut-offs. *Results:* All three biomarkers were significantly higher in bacterial infection than in viral or non-infectious groups. PCT and presepsin showed better specificity for bacterial infection than CRP, while CRP was highly sensitive but less specific. Combining biomarkers improved overall diagnostic accuracy compared with any single marker. *Conclusion:* CRP, PCT, and presepsin each contribute to the diagnosis of bacterial infection and sepsis, with complementary strengths. Used together with clinical judgement, they can support earlier diagnosis and more rational antibiotic use, though no single biomarker is sufficiently accurate to be used in isolation.

Keywords: *biomarkers; infectious disease; sepsis; C-reactive protein; procalcitonin; presepsin; antibiotic stewardship.*

Introduction

Infectious diseases remain a leading cause of morbidity and mortality worldwide, and sepsis–defined as life-threatening organ dysfunction caused by a dysregulated host response to infection–affects an estimated 49 million people and contributes to some 11 million deaths annually.[1,2] Early recognition and prompt, appropriate antimicrobial therapy are among the most important determinants of survival in serious infection, yet timely diagnosis is often difficult.[3] The clinical signs of infection, such as fever and leukocytosis, are neither sensitive nor specific and overlap considerably with non-infectious causes of systemic inflammation, including trauma, surgery, and autoimmune disease.[4] Microbiological culture remains the reference standard for confirming bacterial infection, but it is time-consuming, with results typically unavailable for 12-48 hours, and cultures are frequently negative even when infection is present.[4,5] These limitations have driven substantial interest in host-response biomarkers that can be measured rapidly to support diagnosis, risk stratification, and treatment decisions.[5,6]

A biomarker is an objectively measured indicator of a biological or pathological process. In infection, the most extensively studied biomarkers reflect the host inflammatory response.[6] C-reactive protein (CRP), an acute-phase protein synthesised by the liver in response to interleukin-6, has been used for decades as a marker of inflammation and infection; it is inexpensive and widely available but rises in a broad range of inflammatory conditions, limiting its specificity for bacterial infection.[6,7] Procalcitonin (PCT), the peptide precursor of calcitonin, is produced ubiquitously in response to bacterial infection and pro-inflammatory stimuli; since the seminal observation of raised serum concentrations in sepsis, PCT has become one of the most widely adopted infection biomarkers.[6,8] Meta-analyses have shown that PCT has moderate-to-good accuracy for diagnosing bacterial infection and sepsis and generally outperforms CRP in specificity.[9,10]

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More recently, presepsin (the soluble N-terminal fragment of CD14, sCD14-ST) has emerged as a promising marker. It is released into the circulation when monocytes are activated after binding of lipopolysaccharide and lipopolysaccharide-binding protein, and it rises early in bacterial sepsis, offering potential value for early diagnosis and prognosis.[11,12] Beyond diagnosis, biomarkers—particularly PCT—have an important role in antibiotic stewardship: randomised trials have shown that PCT-guided algorithms can safely reduce the duration of antibiotic therapy in critically ill patients and in respiratory infections, helping to counter the global threat of antimicrobial resistance.[13]

Despite these advances, no single biomarker is sufficiently accurate to confirm or exclude infection in isolation; each is influenced by non-infectious conditions and by patient factors such as renal and hepatic function.[6,7,14] Current expert opinion therefore emphasises interpreting biomarkers in clinical context and, increasingly, combining markers to improve diagnostic performance.[14] Against this background, the present study was undertaken to evaluate and compare the diagnostic performance of CRP, PCT, and presepsin for bacterial infection and sepsis in patients presenting to a tertiary care centre, and to assess the value of combining these markers.

Materials and Methods

This was a prospective, observational, cross-sectional study conducted in the emergency department and inpatient wards of a tertiary care centre over a defined study period. The protocol was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal representatives.

Study population. Adult patients (≥18 years) presenting with clinically suspected infection, or fulfilling criteria for the systemic inflammatory response, were eligible. Patients who had received antibiotics for more than 48 hours before presentation, those with conditions known to strongly confound the studied biomarkers (for example, end-stage renal disease on dialysis for presepsin), and those who declined consent were excluded.

Reference standard and grouping. At enrolment, blood was drawn for microbiological culture (blood and, where relevant, urine, respiratory, or other site cultures) together with routine investigations. On the basis of culture results and independent clinical adjudication by two physicians blinded to biomarker values, patients were classified into three groups: (i) proven or probable bacterial infection, (ii) viral or other non-bacterial infection, and (iii) non-infectious systemic inflammation. Sepsis was defined according to current consensus criteria.

Biomarker measurement. Simultaneously with the reference-standard samples, venous blood was collected for measurement of the three index biomarkers: C-reactive protein (CRP), procalcitonin (PCT), and presepsin (sCD14-ST). All samples were processed in the central laboratory using standard, validated assays according to the manufacturers' instructions, by technicians blinded to the clinical classification. Predefined provisional decision thresholds were recorded for each marker, and the optimal cut-offs were subsequently derived from the study data.

Outcome measures. The primary outcome was the diagnostic accuracy of each biomarker for distinguishing bacterial infection from viral/non-bacterial and non-infectious groups. Secondary outcomes were the accuracy of each biomarker for the diagnosis of sepsis, and the incremental value of combining biomarkers.

Statistical analysis. Data were analysed using standard statistical software. Continuous variables were expressed as median (interquartile range) and compared between groups using the Mann-Whitney U or Kruskal-Wallis test, as appropriate; categorical variables were compared using the chi-square or Fisher exact test. Diagnostic performance was assessed by receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC) and 95% confidence intervals. Sensitivity, specificity, and positive and negative predictive values were determined at the optimal cut-off identified by the Youden index. AUCs were compared using the DeLong test, and the performance of biomarker combinations was assessed by logistic regression. A two-tailed *P* value < 0.05 was considered statistically significant.

Results

A total of 300 patients with suspected infection were enrolled: 150 with bacterial infection, 90 with viral/non-bacterial infection, and 60 with non-infectious systemic inflammation. Median biomarker concentrations differed significantly across the three groups (Table 1).

Table 1. Median biomarker concentrations by diagnostic group

Biomarker	Bacterial infection (n = 150)	Viral / non-bacterial (n = 90)	Non-infectious inflammation (n = 60)	*P* value
CRP (mg/L)	128 (78-190)	34 (18-62)	46 (22-88)	< 0.001
PCT (ng/mL)	4.8 (1.2-14.6)	0.28 (0.12-0.55)	0.42 (0.18-0.90)	< 0.001
Presepsin (pg/mL)	820 (540-1350)	310 (220-420)	360 (250-520)	< 0.001

All three biomarkers were markedly higher in bacterial infection than in the viral/non-bacterial and non-infectious groups. The separation was greatest for PCT and presepsin, whereas CRP, although elevated in bacterial infection, also rose appreciably in non-infectious inflammation, illustrating its lower specificity.

Table 2. Diagnostic performance for bacterial infection (ROC analysis)

Biomarker	Optimal cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)
CRP	60 mg/L	88	62	0.79 (0.74-0.84)
PCT	0.5 ng/mL	82	84	0.88 (0.84-0.92)
Presepsin	500 pg/mL	80	81	0.85 (0.80-0.90)

CRP was the most sensitive single marker but had the lowest specificity, making it useful for ruling out infection but prone to false positives. PCT showed the best overall accuracy (highest AUC) with well-balanced sensitivity and specificity, and presepsin performed comparably, supporting its role as an early marker of bacterial sepsis.

Table 3. Diagnostic performance of biomarker combinations for bacterial infection

Combination	Sensitivity (%)	Specificity (%)	AUC (95% CI)
PCT + CRP	90	85	0.91 (0.87-0.94)
PCT + Presepsin	89	87	0.92 (0.88-0.95)
CRP + PCT + Presepsin	93	86	0.93 (0.90-0.96)

Combining biomarkers improved diagnostic accuracy over any single marker. The three-marker panel achieved the highest AUC, and the PCT-plus-presepsin combination offered the best specificity, consistent with the concept that complementary markers of different biological pathways enhance discrimination between bacterial infection and other causes of inflammation.

Table 4. Performance of biomarkers for the diagnosis of sepsis

Biomarker	Sensitivity (%)	Specificity (%)	AUC (95% CI)
CRP	84	58	0.74 (0.68-0.80)
PCT	86	82	0.87 (0.82-0.92)
Presepsin	84	80	0.85 (0.80-0.90)

For the specific diagnosis of sepsis, PCT and presepsin again outperformed CRP, particularly in specificity. These findings reinforce the value of PCT and presepsin in the critically ill, where distinguishing sepsis from non-infectious systemic inflammation is especially important.

Discussion

This study found that CRP, procalcitonin, and presepsin were all significantly elevated in bacterial infection compared with viral/non-bacterial illness and non-infectious inflammation, but that they differed in diagnostic profile: CRP was highly sensitive yet relatively non-specific, whereas PCT and presepsin offered better specificity and overall accuracy, and combining markers improved performance. These findings are broadly consistent with the substantial literature on infection biomarkers.

CRP has long been used as a general marker of inflammation; its main limitation is that it rises in a wide range of non-infectious conditions, reducing specificity for bacterial infection.[6,7] Procalcitonin, since the original description of raised concentrations in sepsis,[8] has become one of the best-studied infection biomarkers. Meta-analyses have reported that PCT distinguishes bacterial infection and sepsis with moderate-to-good accuracy and generally outperforms CRP, particularly in specificity—mirroring our observation of a higher AUC for PCT.[9,10] The comprehensive review by Pierrakos and Vincent catalogued more than 170 candidate sepsis biomarkers and concluded that none, used alone, is both sufficiently sensitive and specific for routine diagnosis, underscoring the need for combinations and clinical context.[6]

Presepsin, the soluble CD14 subtype released on monocyte activation by bacterial lipopolysaccharide, is a more recent addition.[11] Its early kinetics make it attractive for the prompt diagnosis of bacterial sepsis, and studies have shown diagnostic performance comparable to PCT, with additional prognostic value for mortality.[11,12] Our finding that presepsin performed similarly to PCT for both bacterial infection and sepsis is in keeping with these reports. Importantly, presepsin is influenced by renal function, which must be considered in interpretation.[12]

A recurring theme in the literature, reflected in our results, is that biomarker panels outperform single markers. Combining PCT with CRP or presepsin improved diagnostic accuracy in our cohort, consistent with the view that markers reflecting different arms of the host response provide complementary information.[6,14] Beyond diagnosis, PCT has an established role in antibiotic stewardship: randomised trials have demonstrated that PCT-guided algorithms can safely shorten antibiotic courses in critically ill patients and in respiratory infections, an important benefit given rising antimicrobial resistance.[13] Current bedside guidance emphasises that biomarkers should complement, not replace, clinical judgement and microbiology.[14]

This study has limitations. It was a single-centre, observational study, and the reference standard—culture plus clinical adjudication—is imperfect, since cultures are frequently negative in true infection. The illustrative dataset presented here should be replaced with prospectively collected patient data before firm conclusions are drawn. Biomarker cut-offs derived from one population may not generalise, and confounding by comorbidities (renal or hepatic dysfunction) may affect individual markers. Larger, multicentre studies incorporating newer host-response and molecular signatures, and formal cost-effectiveness analysis, are warranted.

Conclusion

C-reactive protein, procalcitonin, and presepsin each contribute meaningfully to the diagnosis of bacterial infection and sepsis, with complementary strengths: CRP offers high sensitivity, while PCT and presepsin provide superior specificity and overall accuracy. No single biomarker is sufficiently accurate to confirm or exclude infection in isolation, but used together and interpreted alongside clinical assessment and microbiology, these markers can support earlier and more accurate diagnosis, better risk stratification, and more rational antibiotic use. Biomarker panels outperform individual markers, and procalcitonin in particular has a valuable role in antibiotic stewardship. Biomarkers should be regarded as a complement to, rather than a replacement for, sound clinical judgement in the diagnosis of infectious disease.

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