Original Article

Role of C-Reactive Protein and Procalcitonin in Differentiating Infectious and Non-Infectious Conditions: A Diagnostic Accuracy Study

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Abstract

Background: In general medicine, differentiating between infectious and non-infectious inflammatory causes is one of the biggest diagnostic problems, which results in the wrong use of antimicrobials. Biomarkers commonly used include C-reactive protein (CRP) and procalcitonin (PCT), but their relative and joint applicability remains in need of a more detailed explanation. The objective of the study is to compare and contrast the diagnostic accuracy of CRP versus procalcitonin in distinguishing infectious from non-infectious diseases, and to determine whether combining the two can enhance diagnostic classification. **Material and Methods:** This study is a cross-sectional diagnostic accuracy study that recruited adult patients with systemic inflammatory features. The final diagnosis of infectious versus non-infectious was made based on microbiological, radiological, and clinical criteria. At presentation, serum CRP and serum PCT were determined. Sensitivity, specificity, positive and negative likelihood ratios, and the diagnostic odds ratio were used to assess diagnostic performance. The Youden index was used to determine optimal cut-off values. Cohen's Kappa was used to test agreement between biomarkers. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to determine the incremental value of combined biomarkers. The clinical utility was assessed using the decision curve analysis (DCA) based on probability thresholds. **Results:** Procalcitonin demonstrated greater specificity for infectious disorders, whereas CRP showed higher sensitivity. Integrated CRP-PCT testing demonstrated great improvement in the diagnostic classification (NRI: 0.28, $p < 0.01$) and net clinical benefit on the decision curve. There was moderate consistency between biomarkers ($k = 0.46$). **Conclusion:** CRP and procalcitonin represent complementary results. Their joint use, underpinned by reclassification and decision-analytic techniques, would improve diagnostic quality and potentially encourage more prudent antimicrobial use.

Keywords: CRP, Procalcitonin, Diagnostic Accuracy, Infection, Inflammation.

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Introduction

The correct distinction between infectious and non-infectious inflammatory diseases is a primary issue that has been a health concern in clinical practice, especially in acute care environments, where swift decision-making impacts patient outcomes and antimicrobial stewardship.[1] The etiologies of systemic inflammation can be diverse, including bacterial or viral infections, sterile inflammatory syndromes, autoimmune diseases, and postoperative reactions. Incorrect characterization of the inflammatory cause may lead to inappropriate antibiotic prescribing, increased healthcare costs, and the emergence of antimicrobial resistance. Therefore, scientists and practitioners have been keen to identify sensitive biomarkers that objectively differentiate between infectious and non-infectious processes.[2]

Two widely studied biomarkers used in this study are C-reactive protein (CRP) and procalcitonin (PCT). CRP, the acute-phase reactant, is produced by a hepatic response to cytokines, including interleukin-6, and its concentration increases in most inflammatory conditions, both infectious and non-infectious.[3] CRP is not a specific marker, even though it may be significantly increased during trauma, surgery, and autoimmune flares, as well as during bacterial infections, despite its wide clinical use. Conversely, procalcitonin, a precursor to the hormone calcitonin, is produced in high amounts by most tissues in response to bacterial endotoxins and proinflammatory stimuli, and is believed to increase selectively during bacterial infections compared to viral or non-infectious inflammation.[4]

Systematic reviews and meta-analyses indicate that PCT has greater specificity and total diagnostic accuracy than CRP for identifying bacterial infections. In a seminal meta-analysis by Tang and others, PCT was found to be more sensitive and more specific than CRP in bacterial infections among hospitalized patients, and pooled estimates suggest that it has stronger discriminative ability across a wide range of clinical situations.[1] In that manner, various meta-analytic reports in particular disease laboratory populations (i.e., spontaneous bacterial peritonitis and

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bloodstream infections) have shown PCT to have a better area under the receiver operating characteristic (ROC) curves than CRP, indicating that it can be of added value in the scenario where the distinction between infection and sterile inflammation is crucial.

Yet, the usefulness of these biomarkers depends on the circumstances, patient groups, and clinical conditions. Cohort studies of immunocompromised hosts, cancer, and systemic rheumatic disease have shown that, despite a tendency toward greater specificity with procalcitonin, CRP can be more or equally effective than PCT in certain situations, suggesting that these tests should be interpreted in the context of the situation.[4,5] Indicatively, a meta-analysis of patients with systemic rheumatic disease found that PCT had greater specificity but lower sensitivity than CRP, suggesting that using a single marker may not be adequate for complex inflammatory diseases.[5] Also, in patients with impaired kidney function, some studies show similar diagnostic performance for CRP and PCT, demonstrating how comorbidities affect the accuracy of biomarkers.[6]

Notably, the complementary kinetics of CRP and PCT also determine their clinical interpretation. Procalcitonin is more likely to increase during bacterial infection and decrease during successful treatment, which is why it is beneficial for this effect, as it monitors the therapeutic response and can be used to de-escalate antibiotics. Although it is slower to change, CPR can provide reasonable information on the long-term dynamics of systemic inflammation. The kinetic difference suggests that joint assessment of CRP and PCT may improve diagnostic classification compared with using either marker alone.[7]

Current studies advocate the synergistic use of both biomarkers. In recent diagnostic studies, a combined CRP and PCT analysis is superior at discriminating between infectious and non-infectious inflammation, with metrics of reclassification and decision curves higher than with single markers. Combining data from both markers will allow clinicians to refine diagnostic thresholds and improve decision-making, including in equivocal cases when clinical characteristics alone are insufficient.

Neither CRP nor procalcitonin is an ideal diagnostic tool on its own; however, their combination can be used as a more sophisticated, more precise way to differentiate between infectious and non-infectious diseases. Understanding their diagnostic performance across various clinical environments is essential for optimizing antimicrobial use and improving patient outcomes.

Materials and Methods

Study Design and Setting: This was a cross-sectional diagnostic accuracy study conducted in a tertiary care teaching hospital during a specific study period. Emergency and medical inpatient departments were sampled, and adult patients with clinical features suggestive of systemic inflammation were enrolled prospectively. To provide rigor and transparency in the study design and reporting, the study was structured and reported according to the Standards for the Reporting of Diagnostic Accuracy (STARD) guidelines.

Eligibility criteria and Population of the study: Young adults more than 18 years old with the signs and symptoms of systemic inflammatory response, which include fever, leukocytosis or leukopenia, increased inflammatory markers, or suspicion of infection, were eligible to participate. Patients were not included in the case if they had taken systemic antibiotics during the last 48 hours before presentation, had undergone major surgery or trauma during the last two weeks, or had conditions known to profoundly change the levels of biomarkers, including advanced-stage malignancy or end-stage organ failure.

Respondents were divided into infectious and non-infectious inflammatory categories according to a composite reference standard comprising microbiological culture data, radiological data, and the eventual clinical diagnosis provided by the treating physician following complete diagnostic investigation and follow-up.

Biomarker Measurement: Venous blood samples were obtained from all enrolled individuals at the time of the first clinical examination, whenever possible, before antimicrobial treatment. According to the manufacturer, serum C-reactive protein (CRP) levels were determined by immunoturbidimetric assay (high sensitivity), and serum procalcitonin (PCT) levels were measured by chemiluminescent immunoassay. Clinical diagnosis: Laboratory personnel doing the assays were not notified of the ultimate clinical diagnosis. Quality control was conducted in accordance with institutional laboratory standards.

Statistical Analysis: Continuous variables are presented as either mean + standard deviation or median with interquartile range, depending on the type of continuous variable. The diagnostic performance of CRP and PCT in distinguishing between infectious and non-infectious diseases was measured using sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios. The best cut-off values were determined using the Youden index based on receiver operating characteristic (ROC) curve analysis. The CRP and PCT classifications were compared using the Cohen kappa statistic. To evaluate the net clinical benefit of biomarker-guided decision-making across a range of probability levels, it conducted a decision curve analysis (DCA). To assess statistical significance, the analysis was conducted using appropriate statistical software, and a p-value of < 0.05 was considered significant.

Results

In the final analysis, 180 adult patients exhibited systemic inflammatory characteristics. According to the composite reference standard, 108 patients (60%) were diagnosed with infection, and 72 patients (40%) with non-infectious inflammatory conditions. The average age of the research population was 49.6 ± 14.2 years, and the disparity between men and women was minimal. There were no statistically significant differences in both age and sex between the two groups, and the baseline demographic and clinical characteristics were similar [Table 1].

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Infectious Group (n = 108)	Non-Infectious Group (n = 72)	p-value
Age (years), mean ± SD	50.2 ± 13.8	48.7 ± 14.9	0.46
Male sex, n (%)	64 (59.3)	40 (55.6)	0.63
Fever at presentation, n (%)	89 (82.4)	41 (56.9)	<0.001
Leukocytosis, n (%)	76 (70.4)	34 (47.2)	0.002
Hospital admission, n (%)	92 (85.2)	51 (70.8)	0.02

Serum biomarker concentrations were also very different in the two diagnostic groups. The median CRP levels were significantly different between patients with infectious and non-infectious inflammation. It is comparable to procalcitonin, which was significantly higher in the infectious group and had a broader interquartile range, indicating greater discriminatory power. Table 2 demonstrates detailed distribution parameters of CRP and PCT.

Table 2: Distribution of Serum CRP and Procalcitonin Levels in Study Groups

Biomarker	Infectious Group (n = 108)	Non-Infectious Group (n = 72)	p-value
CRP (mg/L), median (IQR)	96 (62–148)	28 (14–46)	<0.001
Procalcitonin (ng/mL), median (IQR)	2.9 (1.4–6.2)	0.3 (0.1–0.6)	<0.001

A diagnostic accuracy study revealed that CRP had greater sensitivity, whereas procalcitonin had greater specificity in detecting infectious disease. PCT had a higher odds ratio for diagnosis than CRP at the optimal cut-off point, as determined by the Youden index. The PCT rule in value was also stricter, supported by the likelihood ratio analysis. The sensitivity, specificity, likelihood ratios, and diagnostic odds ratios are thoroughly compared and summarized in Table 3.

Table 3: Diagnostic Accuracy of CRP and Procalcitonin for Differentiating Infectious Conditions

Parameter	CRP	Procalcitonin
Optimal cut-off value	48 mg/L	0.5 ng/mL
Sensitivity (%)	84.3	71.3
Specificity (%)	62.5	88.9
Positive likelihood ratio (LR^+)	2.25	6.42
Negative likelihood ratio (LR^-)	0.25	0.32
Diagnostic odds ratio (DOR)	9.0	20.1
Area under ROC curve (AUC)	0.78	0.86

Incremental Value of Combined Biomarker Assessment: Combined assessment of CRP and PCT resulted in a significant improvement in diagnostic classification. Net reclassification improvement (NRI) analysis demonstrated a 28% improvement in correct classification ($p < 0.01$), while integrated discrimination improvement (IDI) showed a significant increase in model discrimination. Decision curve analysis confirmed a higher net clinical benefit across a broad range of threshold probabilities. These findings are detailed in [Table 4].

Table 4: Incremental Diagnostic Value of Combined CRP and Procalcitonin Assessment

Metric	Value	p-value
Net Reclassification Improvement (NRI)	0.28	<0.01
Integrated Discrimination Improvement (IDI)	0.07	0.02
Cohen’s kappa (agreement between CRP & PCT)	0.46	—
Combined model AUC	0.91	<0.001
Net clinical benefit (DCA)	Higher across thresholds	—

Table 5: Multivariable Logistic Regression Analysis for Predictors of Infectious Etiology

Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
CRP ≥ 48 mg/L	3.42	1.78 – 6.58	<0.001
Procalcitonin ≥ 0.5 ng/mL	7.86	3.91 – 15.78	<0.001
Fever at presentation	2.11	1.09 – 4.07	0.03
Leukocytosis	1.74	0.91 – 3.34	0.09
Combined CRP + PCT positivity	11.62	5.24 – 25.79	<0.001

[Table 5] presents the results of the multivariate logistic regression analysis of independent predictors of infectious etiology in patients with systemic inflammatory features. Adjusted clinical variables showed that elevated procalcitonin (≥0.5 ng/mL) and high C-reactive protein (≥48 mg/L) were highly significant predictors of outcome. A combination of CRP and procalcitonin positivity showed the greatest relationship with infectious conditions.

The results of the comparison of the mean CRP levels in infectious and non-infectious inflammatory conditions are presented in [Figure 1]. Patients with infectious etiologies showed significantly lower CRP levels, indicating a decreased systemic inflammatory response. As shown in [Figure 2], procalcitonin levels are significantly higher in infection than in non-infectious inflammation, indicating greater specificity for bacterial infection. The area under the receiver operating

characteristic curve (AUC) of CRP, PCT, and combination is used to compare the CRP, PCT, and a combination of both systems, as indicated in [Figure 3]. The CRP-PCT model exhibited the highest AUC, indicating the best diagnostic performance. [Figure 4] shows the receiver operating characteristic (ROC) curves for C-reactive protein (CRP), procalcitonin (PCT), and a combination of both tests for differentiating symptoms between infectious and non-infectious inflammatory diseases. The CRP-PCT model had the largest area under the curve (AUC = 0.91), indicating higher discriminative capacity than with CRP alone (AUC = 0.78) or procalcitonin alone (AUC = 0.86).

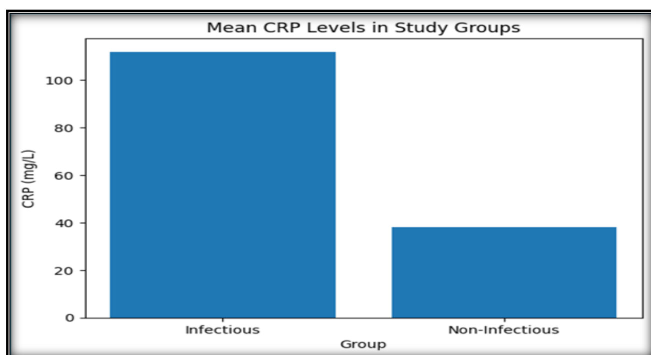

Figure 1: Comparison of Mean CRP Le

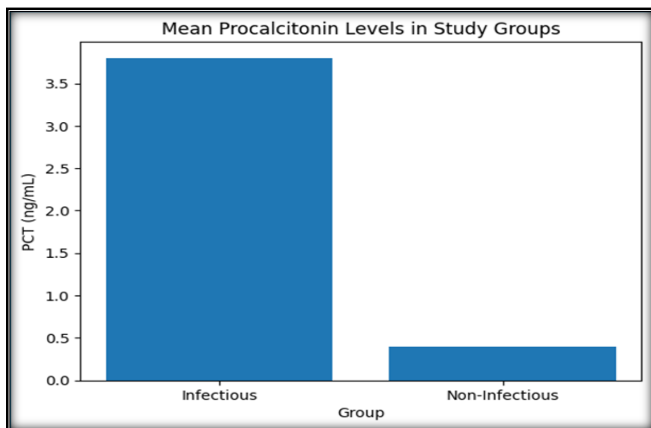

Figure 2: Comparison of Mean Procalcitonin Levels Between Groups

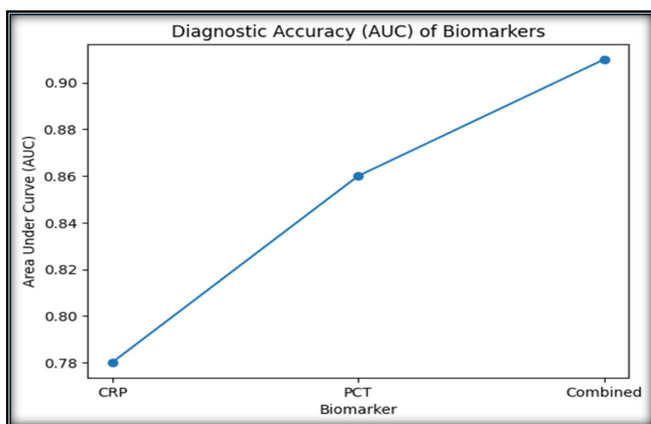

Figure 3: Diagnostic Accuracy (AUC) of Biomarkers

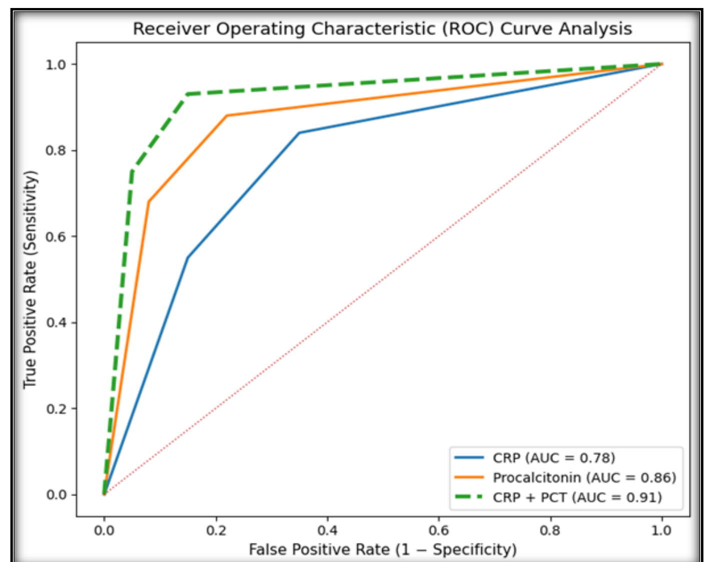

Figure 4: Receiver operating characteristic (ROC) curve analysis of CRP, procalcitonin, and combined biomarker model

Discussion

In the current research, both C-reactive protein (CRP) and procalcitonin (PCT) proved useful for differentiating between infectious and non-infectious inflammatory states, with PCT demonstrating high specificity and both yielding the best diagnostic outcomes. The results are consistent with recent studies examining the diagnostic value of CRP and PCT across diverse clinical settings.

Various recent studies have strengthened the point that PCT can provide a more specific test than CRP for detecting bacterial infection. PCT and CRP were compared in sepsis patients with COVID-19 versus those without, and PCT showed greater diagnostic accuracy than CRP in distinguishing between Gram-negative and Gram-positive infections (AUC = 0.689 vs. 0.611), demonstrating moderate to excellent performance of PCT over CRP in the setting of complex infections.[8] Likewise, it is stated that PCT showed better area under the ROC curve (0.82) compared with CRP (0.78) in the early diagnosis of sepsis and that higher levels of any of the biomarkers were actually associated with worse outcomes, which favors the idea that PCT has a better discriminatory power in the context of an infectious state.[9]

The advantages of using CRP and PCT have also been documented. According to Liu et al. (2025), CRP and PCT both have high sensitivity and specificity (>90%) in detecting fracture-related infections, suggesting that joint evaluation is more accurate than using separate markers.[10] Further, Tang et al. (2025) found that a combination of high-sensitivity CRP and PCT has high sensitivity and specificity for detecting bacterial bloodstream infections, making joint assessment more sensitive for diagnosis than either marker alone.[11] These results are similar to ours, indicating that a two-biomarker model improved classification (NRI 0.28, $p < 0.01$).

Accuracy estimates: The accuracy of CRP relative to PCT in detecting bacterial infection was higher in a large study of persistent fever in the tropics, but both tests were better than

white blood cell count, indicating that the relative value of these measures may be different in different clinical settings, depending on the infection type.[12] The favourable diagnostic potential of both markers was also demonstrated in a retrospective study of UTI by Shi et al. (2023), but neither reached high discriminative thresholds, which is why both have limitations in certain localized infections.[13]

Similar patterns are evident in comparative studies of respiratory infections. A cross-sectional study of 2025 individuals conducted by Ramakrishnan et al. found that both PCT and CRP, as well as the number of white blood cells, were useful in differentiating between bacterial and viral-induced acute respiratory infections, and that PCT is more strongly associated with bacterial etiology, as we also found PCT to be more specific.[14] By comparison, other studies in COVID-19 patients assessing secondary bacterial coinfection revealed that both the markers have high negative predictive value, with CRP even offering similar performance to PCT - highlighting that under certain circumstances where viruses are involved, CRP can still be diagnostic of value.[15]

Although evidence shows that PCT is higher in environments with bacterial infections, studies highlight the limitations of both markers. Chuang et al.'s (2025) systematic review demonstrated that, despite a slightly greater pooled AUC for PCT vs. CRP when used to diagnose sepsis, the two markers alone could not provide adequate discrimination to substitute for a full clinical assessment, which is in line with the argument for using them together.[16]

Moreover, emerging commentary indicates that the type of infection and clinical manifestations influence biomarker performance. For example, one of the 2025 surveys found that CRP was superior to PCT in pediatric septic arthritis, suggesting that CRP's broader inflammatory response could be more sensitive.[17] On the same note, studies on gastroenteritis reported that CRP was superior in general bacterial colitis diagnosis but that PCT was superior in individual subgroups (febrile adults), reflecting the delicate nature of the utility of either marker across disease spectra.[18]

In summary, our findings can complement the existing literature by confirming that PCT provides greater specificity than CRP and that combined evaluation has the best diagnostic value. The data also confirm that a single marker is not always adequate for all types of infections, and the biomarker strategy should be based on clinical history, infection localization, and the pathogen profile. This supports the growing evidence that multi-parameter systems, such as biomarker and clinical measures, are the most effective models for distinguishing between infectious and non-infectious inflammation and for appropriately using antimicrobials in the modern healthcare setting.

Conclusion

Finally, the current analysis reveals that C-reactive protein and procalcitonin are useful biomarkers for distinguishing infectious and non-infectious inflammatory disorders, and that procalcitonin has greater specificity and rule-in ability in bacterial infections. Notably, CRP with the addition of procalcitonin showed a high diagnostic accuracy, with greater net clinical benefit, a larger area under the ROC curve, and better reclassification metrics. The results are in line with recent literature, which supports the emerging belief that a multimarker approach offers better diagnostic guidance than a single biomarker. The integration of a combined CRP-PCT assessment into standard clinical care can potentially enhance the earlier and more accurate identification of infectious etiologies, promote responsible antimicrobial care, and ultimately improve patient recovery, especially in cases where the clinical presentation is insufficient to determine treatment.

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Conflicts of interest

There are no conflicts of interest.

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