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# Evaluation of Procalcitonin and C-Reactive Protein as Biomarkers in Suspected Cases of Sepsis among Patients Attending Emergency Department and ICU of A Tertiary Care Hospital in Western Uttar Pradesh

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## ABSTRACT

**Background:** Sepsis is considered one of the leading causes of morbidity and mortality worldwide. Sepsis investigation tools are designed to assist early identification, however, there is wide variation in predictive values. Procalcitonin (PCT) has features of a biomarker as there is a timely and specific increase in bacterial sepsis.

**Aim:** The study aimed to evaluate the role of PCT and C-reactive protein (CRP) as predictors of sepsis among suspected cases of sepsis.

**Materials and methods:** A prospective observational single-center study was conducted. Patients suspected of sepsis having a fever ≥38ºC at the time of admission, aged ≥18 years were included. Blood samples of subjects for blood cultures, PCT, and CRP levels were obtained. Sensitivity and specificity were measured by taking blood culture as the gold standard.

**Results:** Out of 80 cases included 26 patients had bacterial growth on blood culture. The mean value of PCT in the culture positive and the negative group was 14.62±15.00 and 4.83±7.17 ng/ml respectively. CRP mean levels in the culture positive were 40.22±18.54 and in the culture negative group were 37.82±19.15 mg/L. At a serum PCT cut-off of 4ng/ml, sensitivity and specificity were found to be 76.9% and 72.2% respectively. For a cut-off of 38mg/L, CRP showed a sensitivity of 46.1% and a specificity of 72.2%. Furthermore, ROC analysis showed PCT having an AUC=0.71 performed more efficiently than the AUC=0.54 of CRP.

**Conclusion:** The use of PCT as a tool for diagnosing sepsis proved to be a reliable timely biomarker and more applicable than CRP in patients suggestive of sepsis. Depending on the etiology of the infection, PCT can be a valuable approach in the emergency department.

**Keywords:** Blood culture, C-reactive protein, Procalcitonin, Sepsis, PCT

## INTRODUCTION

Sepsis is considered one of the leading causes of morbidity and mortality worldwide.[1] It is one of the prevalent causes of multiorgan failure.[2] Recently, a global study estimated 48.9 million cases and 11 million deaths due to sepsis, estimated for 20% of all global deaths annually.[3] Sepsis is debated as a disease of complex pathophysiology arising as a result of the host's response to infection.[4] Diagnostic adaptations and changing definitions of sepsis have resulted in an unclear situation regarding the accuracy of sepsis-related observations.[5] Scoring systems used as a diagnostic tool have also shown discrepancies in the reporting methods.[6] It is difficult to characterize sepsis from other conditions as such diagnosing and identifying the illness may be hard.[4] The approach to sepsis and its management have been comprehended

over the years.[5] Sepsis is commonly caused by bacteria but, other causes like viruses, fungi, or parasites are not rare. It can also develop as a result of superinfection in non-infectious conditions.[7] Although, blood cultures can identify bacteria that cause sepsis, several factors limit the number of microorganisms that can be recovered.[8] This is related to the number of organisms present in the patient at a given time or can be due to prior antibiotic use.[9] Sepsis is a life-threatening medical emergency, that is time-dependent and related to unacceptably high fatality rates. The central concept of sepsis therapy is early, rational, and adequate antimicrobial therapy.[10] The difficulty in distinguishing between bacterial and non-bacterial etiologies is one of the main reasons for antibiotic abuse.[11,12] Antibiotic usage that is irrational and prolonged can result in the development of antibiotic-resistant bacteria and lead to numerous harmful consequences.[13] Since sepsis cannot frequently be ruled out, empirical antibiotic therapy is routinely administered.[9] The gold standard for sepsis diagnosis is blood culture however, the results are delayed and take time.[11,14] This delay has led to the development of rapid and helpful testing by the use of biomarkers and molecular methods.[9] Common inflammatory biomarkers like C-reactive protein (CRP), white blood cell count, tumour-necrosing factor-alpha (TNF-α), interleukins, etc. are non-specific for diagnosing sepsis.[15] A conventional biomarker like CRP is an acute-phase protein and as such evidence on the diagnostic precision of CRP to differentiate infection from non-infection is cryptic and uncertain.[14] There is a continuous search for new biomarkers for sepsis and another such promising marker procalcitonin (PCT), a peptide precursor of calcitonin hormone is part of the inflammatory cascade in sepsis, which could be a critical tool for the diagnosis of sepsis and aid to clinicians in deciding antibiotic treatment duration.[11] Procalcitonin has features of a biomarker, as there is a fast and specific increase in sepsis and also it differentiates infections from non-infectious causes of sepsis.[14] The importance of a timely diagnosis and adequate treatment of sepsis is of crucial importance. It is essential to consider that the clinical features of a patient with sepsis might resemble those of a patient with systemic inflammation due to non-infectious causes. It is possible to analyze procalcitonin levels in less time than taken by blood cultures. The present study aimed at evaluating PCT and CRP in suspected cases of sepsis in patients attending the Emergency Department and ICU in a rural tertiary care hospital.

## MATERIALS AND METHODS

**Study Design:** This was a prospective observational study done in a rural setting in North India, conducted in the Department of Microbiology, UPUMS, Saifai, Etawah from January 2020 to June 2021. Estimating the required sample size was done based on sensitivity, substituting the values for sensitivity and prevalence from the study of Ahmed *et al*,[16] our sample exceeded the determined value. Inclusion criteria were age ≥ 18 years both genders, fever T ≥38ºC at the time of presentation and qSOFA assessment by the Emergency Department physicians in clinically suspected sepsis cases, through non-probability sampling. Sepsis was further confirmed by the presence of positive blood culture. Exclusion criteria were patients with a history of cardiogenic shock, burns, malignancy, and trauma. Patients with a history of recent surgery, pancreatitis, and patients on immunotherapy and hemodialysis were also excluded. Demographic and clinical data were recorded for each patient. Patients who gave their written and informed consent were only enrolled.
Ethical approval was obtained from the institutional Ethics Committee letter no.101/2019-20.

**Laboratory workup:** One set of aerobic and anaerobic blood cultures and 5ml of blood was withdrawn from each patient simultaneously for PCT and CRP detection at the time of admission and sent to the microbiology laboratory for further processing. The blood samples for PCT and CRP were centrifuged at 5000 rpm for 5 minutes; serum was collected and aliquots were stored at -70ºC for later use. Repeated freeze-thaw cycles were also avoided. Serum samples in batches were further analyzed for PCT and CRP by ELISA. Identification of bacterial microorganisms from positive blood cultures was done in VITEK® 2 COMPACT (BioMérieux, France) system. Samples were divided into positive and negative blood culture groups. The growth was identified by the following methods-Colony morphology on Blood Agar and MacConkey agar. Coagulase-negative *Staphylococci*, *Micrococcus* species, *Corynebacterium* species, *Bacillus* species, and other skin commensals were not included in the blood culture positive group and were considered contaminants. In the absence of clinical and/or laboratory data suggesting their pathogenic role and also which were not deemed clinically significant by the physician. Such bacterial growth was included in the negative culture group. Commercially available sandwich enzyme-linked immune-sorbent (ELISA) assay kits were used for the determination of PCT (Procalcitonin-EIA-BEST; AO Vector-Best, Russian Federation) and CRP (CRP Ultra EIA; XEMA Co., Ltd, Russia). Assays were done using a microplate ELISA reader (AM 2100, USA).

**Statistical Analysis:** The collected data were transformed into variables, coded, and entered in Microsoft Excel. Data were analyzed and statistically evaluated using SPSS version, 25.0 by IBM, USA.

Quantitative data were expressed in mean±standard deviation or median with interquartile range and depends on normality distribution. The difference between the two comparison groups was tested by Student's t-test. Qualitative data were expressed in percentages and proportions. A p-value of less than 0.05 was considered statistically significant. Diagnostic accuracy of PCT and CRP was calculated based on sensitivity, specificity, PPV, and NPV taking blood

culture as the gold standard. For further analysis, Receiver Operative Characteristic (ROC) curves were plotted for PCT and CRP, and the area under the curve (AUC) was calculated with a 95% confidence interval.

**RESULTS**

In the present study, 80 patients met the inclusion criteria and were further analyzed. Fifty-six percent of the patients were males (n=45). The male-to-female ratio is 1.28:1. The mean age of the group was 55.7 years; a range of 18-90 years. Twenty-six patients (32.5%) showed bacterial growth in blood cultures. Among the various organisms identified on culture *Escherichia coli* (*E. Coli)* (n=9) was the most frequent, presented in Table 1. The various sites of the primary source of infection in culture positive and culture negative groups are presented in Table -2. The lungs were commoner sites of infection in both groups. Urinary tract infection (UTI) and skin wound/cellulitis were less common in culture negative than in culture-positive patients. PCT and CRP levels in all the patients were measured.

**Table 1: Distribution of serum PCT and CRP concentrations corresponding to different causative pathogens in culture positive cases.**

| **Type of bacteria** | | **No. of isolates n (%)** | **PCT** | **CRP** |
|---|---|---|---|---|
| **Gram +ve** | | | | |
| *Staphylococcus aureus* | | 5 (19.2%) | 4.06 (0.06-6.06) | 38.22 (23.67-65.15) |
| **Gram -ve** | | 21 (80.7%) | 9.66 (5.85-32.95) | 35.91 (26.20-54.97) |
| **Enterobacteriaceae (n=15)** | *E. Coli* | 9 (34.6%) | 18.22 (4.56-36.35) | 31.73 (22.27-56.56) |
| | *Klebsiella pneumoniae* | 6 (23%) | 17.43 (6.94-43.26) | 33.18 (26.38-45.09) |
| **NFGNB (n=6)** | *Acinetobacter baumannii* | 2 (7.7%) | 11.75±4.01 | 55.34±9.72 |
| | *Pseudomonas aeruginosa* | 4 (15.3%) | 5.85 (1.26-11.12) | 32.56 (19.70-60.17) |

**Table 2: Source of infection in patients with blood culture positive and culture negative sepsis.**

| **Source of infection** | **Culture positive (n=26)** | **Culture negative (n=54)** |
|---|---|---|
| **Pneumonia** | 9 (34.6%) | 19 (35.1%) |
| **UTI** | 8 (30.7%) | 11 (20.3%) |
| **Skin wound/cellulitis** | 4 (15.3%) | 6 (11.1%) |
| **Meningitis** | 3 (11.5%) | 8 (14.8%) |
| **Biliary tract infection** | 3 (11.5%) | 1 (1.8%) |
| **Abdominal/Liver abscess** | 2 (7.7%) | 6 (11.1%) |
| **Gastrointestinal infection** | 1 (3.8%) | 7 (13%) |

**Table 3: Comparison of PCT and CRP in culture positive and culture negative groups.**

| **Biomarker** | **Culture positive group** | **Culture negative group** | **P value** |
|---|---|---|---|
| **PCT mean ng/ml** | 14.62±15.00 | 4.83±7.17 | **0.0001** |
| **CRP mean mg/L** | 40.22±18.54 | 37.82±19.15 | **0.672** |

**Table 4: Comparison of Diagnostic performance of PCT and CRP for diagnosis of sepsis.**

| | **PCT** | **CRP** |
|---|---|---|
| **AUC** | 0.717 | 0.544 |
| **95% CI** | 0.61-0.80 | 0.44-0.64 |
| **Cut off value** | 4 | 38 |
| **Sensitivity** | 76.9% | 46.1% |
| **Specificity** | 72.2% | 72.2% |
| **PPV** | 57.1% | 44.4% |
| **NPV** | 86.6% | 73.6% |
| **Accuracy** | 73.7% | 63.7% |

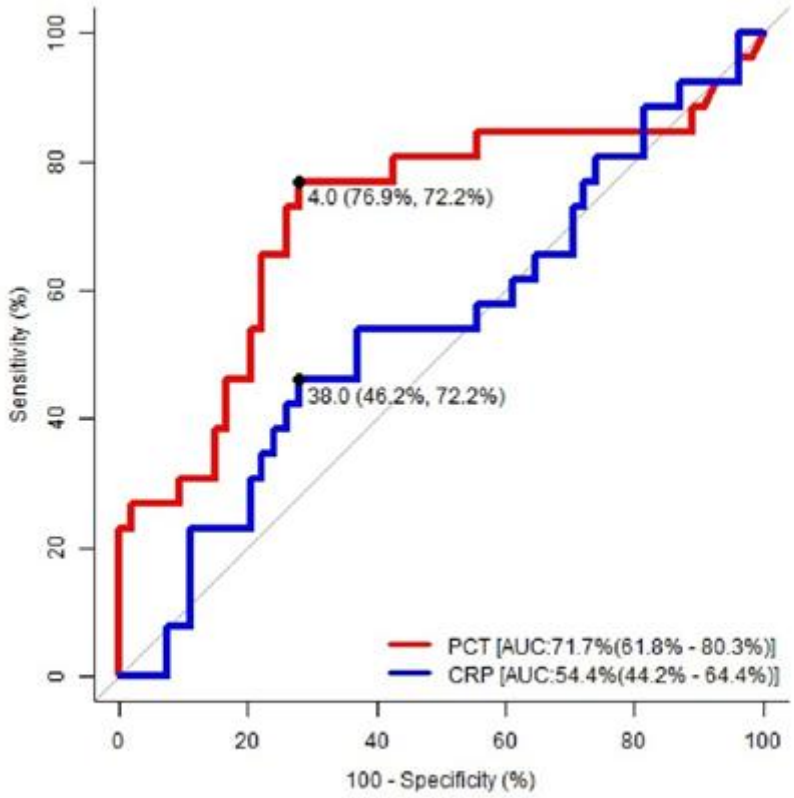


**Figure 1: ROC analysis of PCT and CRP against blood culture positive as gold standard.**

The mean PCT level in the culture positive group was 14.62 ± 15.00 ng/ml and in the culture negative group was 4.83±7.17 ng/ml, which was a statistically significant difference (p=0.0001). There were no significant differences between the culture positive and culture negative groups concerning CRP levels (p=0.672), presented in Table 3. To evaluate the sensitivity and specificity of PCT and CRP, receiver operating ROC curves were calculated compared to culture as the gold standard. The area under the curve AUC for PCT was 0.717 (95% CI 0.618-0.803) and the optimal cutoff value of PCT for predicting a positive blood culture was 4 ng/ml. Using this cutoff value, the sensitivity, specificity, PPV, NPV were 76.9%, 72.2%, 57.1% and 86.6% respectively. The best cutoff value for CRP was 38 mg/L, at which it showed a sensitivity, specificity, PPV, NPV, and AUC of 46.1%, 72.2%,44.4%, 73.6%, and 0.544 (95% CI 0.442-0.644) respectively, presented in Figure 1 and Table 4.

## DISCUSSION

Clinicians continue to face adversities in detecting infections early. In patients presenting with sepsis, routine laboratory tests typically lack both sensitivity and specificity in determining which individuals should be treated with antibiotics.[15] To date blood culture has been the standard concerning detecting bacteria in blood but lacks timely availability and further shows decreased sensitivity.[9] Biomarkers for sepsis diagnosis might allow for early management and minimize the chance of mortality.[15] In the present study, we included 80 suspected cases of sepsis. Among these cases 45 (56.2%) were male and 35 (43.7%) were female. Gender distribution in our study demonstrated maximum male cases. This finding has been consistently reported in all the large epidemiologic studies in ICU patients.[17,18] In this study, blood cultures were positive in 26 patients(32.5%). Similar low prevalence results are also reported by other studies.[19,20] On the contrary higher percentages have been reported in most prior research studies.[12,16,21] Low blood culture rate in our study may be attributed to the small sample size and the culture negative patients could have received antibiotics before admission. Repeat blood culture samples taken in other studies may reflect their high positivity rate. Other conceivable explanations could be sampling methodologies, the inadequate volume of blood, poor transport access to the laboratory, and slow-growing bacteria.[1] Negative culture should not offer the physician false optimism; patients are still at risk of dying.[8] Among the total blood culture positive cases (26) we found more Gram-negative pathogens, this result is concordant with various published studies.[12,21,22] A study done by Prakash KP *et al*., have found a predominance of Gram-positive bacteria.[23] The PCT levels in our study in gram-negative bacteria were higher than those in gram-positive

bacteria. This was in agreement with the reports of Nargis *et* al., and Li S *et al.*[11,14] This could be explained by the difference in the cell wall composition of gram positive and gram-negative bacteria and different pathogen-associated molecular patterns, engaging different Toll-like receptors, expressed on host cells.[4,24] Amongst the gram-negative bacilli (GNB), Enterobacteriaceae and non-fermenting gram-negative bacilli (*P. aeruginosa* and *A. baumannii*) were the etiological agents. *E. coli* had the highest 18.22 (4.56-36.35) ng/ml median PCT value, while infection due to non-fermenters like *P. aeruginosa* exhibited a median of 5.85 (1.26-11.12) ng/ml. This finding is concordant with a prior study that has also reported higher PCT levels induced by Enterobacteriaceae as compared to non-fermentative GNB.[25] However, Gupta *et al*., reported moderate PCT levels in gram positive bacteria.[21] These results signify that PCT could distinguish bacterial types and assist in decisions on the use of ideal antimicrobial therapy. The predominant source of infection in our study in both culture positive as well as culture negative patients was respiratory followed by urinary tract infection. This finding concurs with previous studies that reported lung infection as the highest source of development of infection in culture positive and culture negative patients.[1,13] Knowledge of the most prevalent bacteria that cause sepsis based on the location of infection can help us choose an appropriate empirical antibiotic.[13] Common pathogens that can develop into sepsis based on the source of infection are reported by prior studies.[9,13,23] To overcome the inherent inferiorities of blood culture as a diagnostic tool to differentiate between blood culture positive and blood culture negative sepsis, PCT and CRP have been studied and found to have their impact in their respective ways.[26] We noted that PCT and CRP levels vary between groups with one of the major findings in our study that includes PCT threshold for ruling out sepsis compared with blood culture. Serum levels of PCT in our study showed significant ($p=0.0001$) raised mean values of 14.62±15.00 ng/ml in culture positive group, this tells that it can be used as an early diagnostic marker in the emergency before culture results are available. Although CRP is known as a sensitive marker of infection and inflammation, in the present study there was no significant difference between mean concentrations of culture positive 40.22±18.54 mg/L and negative groups 37.82±19.15 mg/L. A previous study reported similar significant mean values in the bacteremic group for PCT and non-significant for CRP.[25] We also agree with the belief reported by Chan *et al*., that each biomarker performance is closely associated with the characteristics of the study subjects and the clinical settings with a difference in the inflammatory effects produced by the biomarker.[15] According to several research studies, combining PCT with CRP testing is the most reliable diagnostic approach.[27] To evaluate the sensitivity and specificity of PCT and CRP receiver operating curves (ROC) were calculated compared to blood culture. The findings of the present study revealed that serum PCT cutoff of 4 ng/ml was highly suggestive of culture positive sepsis with good sensitivity (76.9%), specificity (72.2%), PPV of 57.1%, and NPV of 86.6%. In our study, a CRP cutoff at 38 mg/L showed a sensitivity of 46.1% and specificity of 72.2% with a disappointingly low PPV of 44.4% and NPV of 73.6%. Moreover, the AUC of PCT was significantly higher than that of CRP AUC 0.717 (95% CI0.61-0.80) vs 0.544 (95%CI 0.44-0.64), suggesting that PCT is superior to CRP as a marker for identifying and diagnosing sepsis, which was consistent with the findings of Joen JS *et al*.[28] Based on statistical considerations, these cutoff values were conserved because they were the optimal compromise between sensitivity and specificity as predicted on the ROC curve. However, in clinical practice, the threshold should be appropriate for the clinical situation. Many studies have been performed to determine the cutoff value of PCT for predicting a positive blood culture, but the results are varied.[26] PCT concentrations are considerably below 0.1 ng/ml in healthy individuals.[15] Plasma PCT levels are decreased in patients with viral and localized bacterial infections than in those with systemic bacterial infections.[29] A study done by Nargis *et al*., have reported mortality confined to the cases with PCT level of > 10ng/ml.[14] The PCT threshold employed by ICUs throughout the world to diagnose sepsis differs substantially.[16] Thus, larger observational and interventional studies are needed to eliminate these discrepancies. Also, the difference in etiologies and severity of a disease add constraints in detecting standardized PCT levels in varied demographic groups.[1,22] Clinicians must note that procalcitonin tests can produce false positives and negatives and that sepsis is a complicated and heterogeneous condition.[30] Because of the varying methodology due to shortcomings of the sepsis definitions used so far, new clinical diagnostic tools available since 2016, the influence of disease time course, different timings of inclusion of PCT and CRP tests after admission, and interpretation criteria utilized for the assays between different investigations, comparing PCT and CRP can be difficult.[5] There are various limitations to our research. Ours was a single-center study and considering a small sample size limiting the power of the study, results may not be generalizable and extrapolated to other populations. Another limitation of our study is serial measurements of PCT and CRP were not performed as such we could not report levels associated with mortality. Causes of sepsis due to other microorganisms were not found. We, therefore suggest validating the predictive performance of PCT and CRP in future prospective studies.

## CONCLUSION

PCT as a biomarker appears to have great relevance in diagnosing or ruling out an infection particularly for triaging decisions. In our study, PCT proved to be a reliable marker for predicting sepsis and is more applicable than CRP in patients with a positive blood culture. Varied sensitivities and specificities imply a different clinical use for both PCT and CRP. Our study identified a modest discriminative value of PCT with significant differences between culture negative and culture positive sepsis. PCT levels can be beneficial in determining the most effective antimicrobial therapy when

blood culture results are unavailable or the infection site is unknown. Gram negative septicemia had significantly higher PCT levels than Gram positive, indicating that PCT is useful in distinguishing Gram negative from Gram positive bacterial infections, also providing additional, beneficial information on the etiology. It can support to guide the initiation of antibiotic therapy based on the ability of PCT to differentiate bacterial species as evidenced by the present study. PCT can improve and complement the predictive power of routinely applied sepsis parameters. Although neither marker can be alone used to distinguish an infectious from a non-infectious clinical syndrome, we recommend more extensive observational and interventional comparing algorithms to best determine the role of PCT as a biomarker in bacterial sepsis.

## CONCLUSION

The implications of our findings are to improve early sepsis diagnosis by the use of biomarkers like PCT when cultures are unrevealing in the majority.

## DECLARATIONS:

**Conflicts of interest: There is no any conflict of interest associated with this study**

**Consent to participate:** There is consent to participate.

**Consent for publication:** There is consent for the publication of this paper.

**Authors' contributions: Author equally contributed the work.**

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