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# Diagnostic and prognostic role of Procalcitonin in sepsis in a tertiary care hospital.

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**Abstract**

***Background:*** **Bacterial sepsis is one of the common causes of morbidity and mortality in patients admitted to any tertiary care hospital. Early diagnosis of bacterial sepsis is a challenge to the clinician and the laboratory. Blood culture is the gold standard for the diagnosis of bacterial sepsis. Isolating the bacteria and determining its antibiotic susceptibility takes a minimum of 48 hours. There is a constant search for biochemical markers which might rapidly indicate bacterial sepsis.**

***Aim:*** **The aim of the study was to evaluate the diagnostic and prognostic role of procalcitonin in bacterial sepsis.**

***Subject and methods:*** **Procalcitonin (PCT) levels were determined in 136 patients admitted to the hospital with symptoms of sepsis. PCT was measured in serum samples obtained from the patients at the same time when blood was drawn for culture.**

***Results:*** **Out of the 136 patients clinically diagnosed with sepsis, 14 patients had a positive blood culture (10.3%). Procalcitonin levels of >0.5 ng/ml was considered as positive. Out of the 14 patients with a positive blood culture, 12 had PCT levels greater than 0.5 ng/ml. ROC analysis revealed maximum sensitivity of 64% and a specificity of 65% with a PCT value of 3.25 ng/ml. The mean PCT values in survivors were lower when compared to PCT values in non survivors.**

***Conclusion:*** **Markers for rapid diagnosis of sepsis is required to institute rapid and appropriate management. Procalcitonin level is one such promising target marker for early diagnosis of sepsis.**

**Keywords**: Procalcitonin, Bacterial sepsis, Blood culture.

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## Introduction

Bacterial sepsis is associated with high morbidity and mortality. Sepsis is the second most common cause of death after myocardial infarction in patients admitted to intensive care units. Mortality due to sepsis is as high as 25-35% and is higher in patients with septic shock [1]. Early diagnosis is critical in management of patients with bacterial sepsis since appropriate antibiotics can be initiated immediately. Blood culture remains the gold standard for diagnosis of bacterial sepsis. However a major limitation is unavailability of results within 48 hrs. Prior antibiotic therapy often results in a negative blood culture there by negating a confirmatory diagnosis of sepsis. Skin colonizers often confound a culture outcome in patients presenting with fever due to non-bacterial causes, resulting in unnecessary antibiotic therapy. Several clinical markers of infection have been recommended but most are found to be non-specific since they can be positive in systemic inflammation of non-infectious origin. Hematological markers of infection like total and differential counts may also be non-specific [2,3,4].

There is a continuous search for biomarkers of sepsis. Some of the biomarkers that have been evaluated include lactate, interleukins, C reactive protein (CRP) and procalcitonin [4,5,6]. C reactive protein is most widely used acute phase reactant and a sensitive marker of inflammation. It cannot differentiate bacterial sepsis from other causes of inflammation. CRP gets elevated only 24 to 48 h after the infection is initiated, hence cannot be a rapid indicator [7,8]. Reports of Procalcitonin (PCT) include its role in diagnosis of bacterial sepsis, determining the severity of sepsis and in determining the duration of antibiotic

administration in children and adults [2,9]. This study was designed to determine procalcitonin levels in patients with sepsis and its correlation with blood culture outcome.

## Materials and Methods

The study was a retrospective study. 136 adult patients (>18 years of age) admitted to a tertiary care hospital between November 2012 to May 2014 were included in the study. The sample size was calculated by taking into account the prevalence of suspected cases of sepsis, sensitivity and specificity of Procalcitonin (PCT). The study was approved by the institutional ethical committee.

### *Materials*

Data on clinical features, laboratory investigations, blood culture and PCT values were retrieved from the medical records department of the institute. A diagnosis of sepsis was made based on the recommendations of the American College of Chest Physicians (ACCP) which included presence of any of the following -2 or more of the features along with suspected or proven source of infection: Temp >38°C (100.4°F) or <36°C (96.8°F), Heart Rate >90, Respiratory Rate >20 or $PaCO_2$ <32 mmHg, WBC >12,000/$mm^3$, <4,000/$mm^3$, or >10% bands. Patients with cardiogenic shock, small cell lung carcinoma, medullary carcinoma of thyroid, major trauma, major surgical intervention, severe burns were excluded from the study, as PCT is nonspecifically elevated in these conditions.

### *Methods*

Blood culture of all 136 patients was done by automated BacT/Alert system. Procalcitonin was measured in Roche e411 Electrochemiluminescence (ECLIA) automated analyzer using PCT kit from B.R.A.H.M.S Diagnostica, Berlin, Germany. According to the manufacturers, a value of PCT >0.5 ng/ml was taken as pathological, 0.5 to 2 ng/ml indicated that systemic infection could not be ruled out, 2 to 10 ng/ml indicated greater chances of sepsis and a value of PCT above 10 ng/ml indicated severe bacterial sepsis.

## Statistical Analysis

Validation of PCT was done by calculating the sensitivity, specificity, positive predictive value, negative predictive value. The cut off value of PCT which gave maximum sensitivity and specificity were calculated by Receiver operator curve (ROC) analysis.

## Results

Blood culture positivity and the bacteria isolated in different ranges of PCT values are given in Table 1. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of PCT by taking a cut off of 0.5 ng/ml or more as positive for sepsis are given in Table 2. Receiver operator curve (ROC) analysis was done to determine the cut off value of PCT for which maximum sensitivity and specificity was obtained. ROC analysis is illustrated in Figure 1 which indicates a maximum sensitivity of 64% and specificity of 65% at PCT value of 3.25 ng/ml.

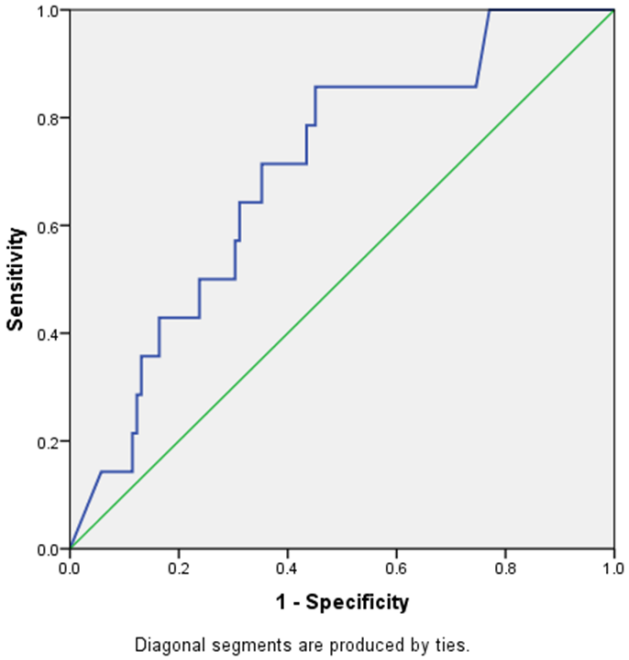


***Figure 1**: Reciver operator curve analysis of PCT levels in patients with sepsis with sensitivity on Y axis and specificity on X axis.*

***Table 1**: Serum PCT values, blood culture results in 136 patients of sepsis.*

| PCT Values | <0.5 ng/ml | 0.5 to 1.9 ng/ml | 2 to 10 ng/ml | >10 ng/ml |
|---|---|---|---|---|
| Total number of patients in number and percentage | 35 (26%) | 37(27%) | 27(20%) | 37 (27%) |
| Blood culture positives in patients in number and percentage | 2 (14%) | 2 (14%) | 3 (22%) | 7(50%) |
| Bacteria grown | *E. coli*, CONS | *K. pneumonia, A. baumanni* | *S. aureus, Acinetobacter, E. coli* | *M. morganii*, *P. aeruginosa*, *E. coli*, *Acinetobacter Escherichia coli* Gram negative bacilli *P. aeruginosa* |

*E. coli: Escherichia coli, CONS: Coagulase negative Staphylococcus aureus, K. pneumonia: Klebsiellapneumoniae, A. baumanni: Acinetobacterbaumanni, S. aureus: Staphylococcus aureus, M. morganii: Morganellamorganii, P. aeruginosa: Pseudomonas aeruginosa*

***Table 2**: Sensitivity, specificity, PPV, NPV of PCT.*

| | |
|---|---|
| Sensitivity (True positives) | 85.7% |
| Specificity (True negatives) | 25.4% |
| PPV | 11.7% |
| NPV | 93.9% |

## Discussion

PCT is the precursor for the hormone calcitonin. Calcitonin has a metabolic role in calcium homeostasis. Though PCT is synthesized in the thyroid and pulmonary cells in normal conditions, all tissues throughout the body have the potential to express PCT [10]. Procalcitonin has been studied as a diagnostic marker in many conditions like fever of unknown origin, meningitis, respiratory tract infections, urinary tract infections, burns and blood stream infections. PCT has been studied as prognostic marker with high values indicating bacterial load and severity of sepsis. The concept of PCT clearance has been used as an indicator of recovery [11].

In the present study, by taking a cut off of >0.5 ng/ml as an indicator of sepsis, the sensitivity, specificity, PPV and NPV was found to be 85.7%, 25.4%, 11.7% and 93.9% (Table 2) and by taking a cut off of >2 ng/ml, the sensitivity, specificity, PPV and NPV was found to be 71.4%, 56.6%, 15.9% and 94.5% . Sinha M et al., observed a sensitivity of 90% and specificity of 84% for a cut off of 0.5 ng/ml where as a sensitivity of 85.7% and specificity of 94.7% was noted with cut off of 2 ng/ml. They concluded that PCT assay may avoid unwarranted antibiotic usage [12]. Harbarth et.al., observed a sensitivity of 97% and specificity of 78% when a cut off of 1.1 ng/ml was used to diagnose systemic inflammatory response syndrome [SIRS] with a conclusion that PCT appeared to be a promising indicator of sepsis in newly admitted, critically ill patients and PCT values complemented with the clinical signs and routine laboratory parameters, suggestive of severe infection [5]. Sudhir U et al., observed that a sensitivity of 94% had a significant association between serum PCT and Sequential Organ Failure Assessment (SOFA) score [13].

Out of the 136 cases, 90 were males and 46 were females. The mean PCT values in males were 15.9 ng/ml and the mean PCT values in females were 13.9 ng/ml. The difference was not statistically significant. Out of the 136 cases, 14 patients had a positive blood culture. Commonest bacteria grown were *Escherichia coli* in 4 out of 14 culture positive cases (Table 1 and Figure 2). Sucilathangam G et al., observed Acinetobacter as the commonest organism grown in 5 out of 14 culture positive cases [14]. Endotoxins present in the bacterial cell wall induce the production of PCT from the parenchymal tissues. The defense response to infection also contributes to increase in PCT levels in bacterial infections. The parenchymal cells do not have the ability to convert PCT to calcitonin leading on to its increased levels in circulation [16,17]. Sinha M et al., observed gram positive cocci as the commonest isolates [12]. Findings of Wang H et al., showed *Escherichia coli*

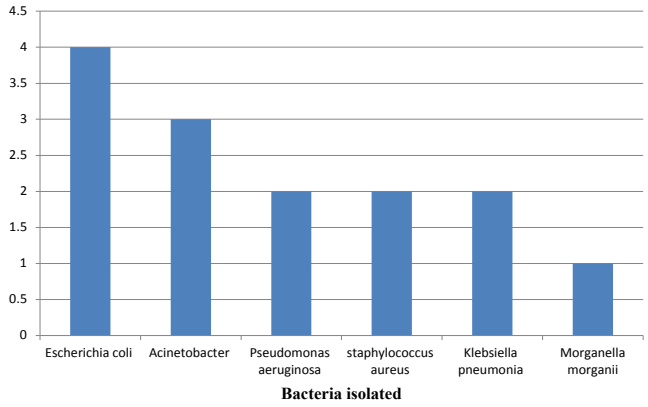


***Figure 2**: Bacteria isolated indicating the most common bacteria isolated in culture was E.coli followed by Acinetobacter, Pseudomonas aeruginosa, staphylococcus aureus, Kliebsiella pneumonia and morganella morganii.*

to be predominant isolate among gram negative organisms similar to the present study. Coagulase-Negative Staphylococcus and Enterococcus were the common gram positive isolates [18]. In the present study, we observed that out of 14 isolates, 12 were gram negative and only 2 isolates were gram positive. A possible correlation between gram negative endotoxins and PCT levels needs to be explored. The mean PCT values of patients with gram positive isolates and gram negative isolates were 2.9 ng/ml and 31 ng/ml but the difference in the values in the two groups were not statistically significant. (Table 3)

ROC analysis revealed, maximum sensitivity of 64% and maximum specificity of 65% for a PCT value of 3.25 ng/ml (Figure 1). In a study done by Riedel S et al., maximum sensitivity and specificity was observed for a much lower value of PCT at 0.1475 ng/ml [15].

The mean PCT value of those who succumbed to the infection (23 in number) was 30.6 ng/ml whereas the mean value in survivors was 12 ng/ml (Table 4). Our findings suggest that high PCT values can indicate high mortality rate when compared to patients with lower values, a finding similar to Jensen J.U et.al., who observed that high PCT levels is an independent predictor of mortality [19]. On the other hand, Ruiz-Alvarez et.al, observed that PCT did not predict mortality whereas CRP did [20]. Pettila et al., observed that there was statistically significant difference in the PCT values measured on first and second days in patients who survived than patients who did not survive [21].

***Table 3**: PCT values in gram positive and gram negative isolates.*

| Isolate | Mean PCT values (ng/ml) ± Standard error of mean | P value |
|---|---|---|
| Gram negative isolate | 31 ± 10 | 0.306 |
| Gram positive isolate | 2.9 ± 2.5 | |

***Table 4**: PCT values in survivors and non survivors.*

| | Mean PCT values (ng/ml) ± Standard error of mean | P value |
|---|---|---|
| Survivors | 12 ± 2.3 | 0.042* |
| Non Survivors | 30.6 ± 8.3 | |

***Table 5**: PCT values in patients with less than 10 days duration of hospitalization and more than 10 days of hospitalization.*

| | Mean PCT values (ng/ml) ± Standard error of mean | P value |
|---|---|---|
| Patients with less than 10 days duration of hospitalization | 15.7 ± 3.3 | 0.79 |
| Patients with more than 10 days duration of hospitalization | 14.5 ± 3.5 | |

It was observed that the mean PCT values of patients (80 in number) who were hospitalized for less than 10 days was 15.7 ng/ml whereas mean PCT values of patients hospitalized for more than 10 days was 14.5 ng/ml (Table 5). Two patients were culture positive but had PCT values within normal range. The isolate from blood of one of the patients was CONS, a normal skin commensal which might not have induced the production of PCT. In another case, a bacterium grown was *E. coli* and PCT was negative. The reason could have been initiation of empiric antibiotic prior to blood culture. It was observed that as the level of PCT increased, the chances of blood culture positivity increased.

## Conclusion

Bacterial sepsis is often a medical emergency requiring intensive management with specific antibiotic therapy and other supportive measures. A delay in detection of sepsis may lead to poor outcome. Rapid sepsis markers in the blood will help in overcoming the limitations of confirmation by blood culture. Procalcitonin levels can play a major role in not only detecting sepsis but also to monitor progress or predict outcome.

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