

# Procalcitonin: A unique marker to evaluate the severity of sepsis among diabetic patients

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## Abstract:

**Introduction:** Diabetes mellitus (DM) is considered one of the largest emerging threats to health and bacterial infections are more frequent in diabetic patients causing sepsis. Several indicators have been proposed as new diagnostic tests to assess sepsis in hospitalized patients.

**Aim:** This study aims to compare the efficacy of Procalcitonin (PCT) and high sensitive C-reactive protein (hs-CRP) in the diagnosis of sepsis in diabetic patients.

**Methods:** In this cross-sectional study total of 60 age and sex-matched diabetic patients above 18 years were randomly chosen with at least 2 SIRS (Systemic inflammatory response syndrome) criteria from the indoor department of BIRDEM General Hospital. Basic hematological, biochemical, microbiological laboratory data were recorded from laboratory reports. Sepsis and its different stages were determined according to American College of Chest Physicians (ACCP) guidelines. The PCT was measured by sandwich enzyme immunoassay (Bio-Vendor, Germany) and the hs-CRP level was measured using an immune-turbidimetric assay (Beckman, Carlsbad, CA 92010, USA).

**Results:** The patient's mean age was 51.90±9.89 years where male 51.2% and female 48.8% and 50-60 years age group was the most common 40%. 38 (63.33%) patients were bacteriological culture-positive and 22 (36.67%) patients were bacteriological culture-negative where the most common organism was *Klebsiella* (28.95%). Statistically, a significant difference was found in PCT values in the bacteriological culture positive and negative group ( $p < 0.05$ ), but there was no significant difference found in hs-CRP values ( $p > 0.05$ ). There was an increasing trend of serum PCT with the developing stages of sepsis. Receiver operating characteristic curve shows the area under the curve for PCT was 0.785 (95% CI; 0.654-0.915), sensitivity 89.47%, specificity 50%, PPV 75.55% and NPV 73.33% with the best cut-off value  $> 753 \text{ pg/ml}$  which support PCT as a superior and reliable marker of sepsis.

**Conclusion:** Our results suggest that serum PCT is a more reliable diagnostic marker of sepsis than other traditional markers like hs-CRP. Combinatorial use of these biomarkers will help in early diagnosis and also greatly improve outcomes.

**Key words:** Procalcitonin, High sensitive C-reactive protein, Sepsis.

## Introduction:

DM is considered one of the largest emerging threats to health in the 21st century and under half a billion people are living with diabetes worldwide and the number is projected to increase by 25% in 2030 and 51% in 2045<sup>1</sup>. Bacterial infections are more frequent and/or serious in patients with diabetes mellitus, which potentially increases their morbidity and mortality also<sup>2</sup>. The greater frequency of infections in diabetic patients is caused by the hyperglycemic environment that favors immune dysfunction<sup>3</sup>. Other causes of infection are a decrease in the antibacterial activity of urine, gastrointestinal and urinary tract motility disturbance and a greater number of medical interventions in these patients<sup>4</sup>. This microbial invasion produces systemic illness referred to as "Sepsis" which encompasses a spectrum of illnesses that ranges from minor signs and symptoms through to organ dysfunction and shock<sup>5</sup>. Impairment in antimicrobial activity

by the host immune system commonly found in both sepsis and diabetes contributes to worsening the host response in diabetic patients with sepsis<sup>6</sup>. Though we have new treatment modalities, advanced laboratory techniques and clinical experience, mortality rates in sepsis are still higher<sup>7</sup>. Hospital mortality in patients of Bangladesh suffering from severe sepsis was 49.2% which is very higher than in other countries<sup>8</sup>. The incidence of sepsis and the number of sepsis-related deaths are increasing day by day and among hospitalized patients by 8.7% per year<sup>9</sup>. The clinical picture is explained by the pathophysiological role of various cytokines, host-derived peptides released in response to a wide variety of immune stimuli. Physicians use various clinical and laboratory data to differentiate infectious from noninfectious conditions in newly admitted patients. But no single clinical or biological indicator of sepsis has gained unanimous acceptance. Though blood culture is the gold standard and has higher sensitivity and specificity over the hematological value

and cytokine levels. But this highly sensitive microbiological parameter is not available in our community health situation and it is time-consuming also. In these cases, several indicators have been proposed as new diagnostic tests to assess sepsis in hospitalized patient. The ability to diagnose or exclude suspected sepsis is vitally important for patient outcomes. PCT and hs-CRP are the most frequently used biomarkers for patients in whom sepsis is suspected<sup>10</sup>. PCT is usually considered to have a higher capacity than hs-CRP in the diagnosis of sepsis<sup>11</sup>. Commonly hs-CRP is used to diagnose and monitor prognosis sepsis in patients. However, in diabetic patients usefulness of PCT over hs-CRP in diagnosing sepsis has not been investigated. We hereby performed this study to compare the efficacy of PCT and hs-CRP in the diagnosis of sepsis in patients.

**Materials and Methods:**

This prospective cross-sectional study was conducted at BIRDEM General Hospital, Dhaka for one year. Total 60 age and sex-matched diabetic patients were randomly chosen with at least 2 SIRS (Systemic inflammatory response syndrome) criteria from the indoor department of BIRDEM General Hospital. All of them were above 18 years and after taking full medical history all of them were examined properly and all medical data were reviewed. All blood samples were drawn within 12 hours of hospital admission. Basic hematological, biochemical, microbiological laboratory data were recorded from laboratory reports. Sepsis and its different stages were determined according to the American College of Chest Physicians (ACCP) definition which is now widely used<sup>12</sup>. The PCT was measured by sandwich enzyme immunoassay

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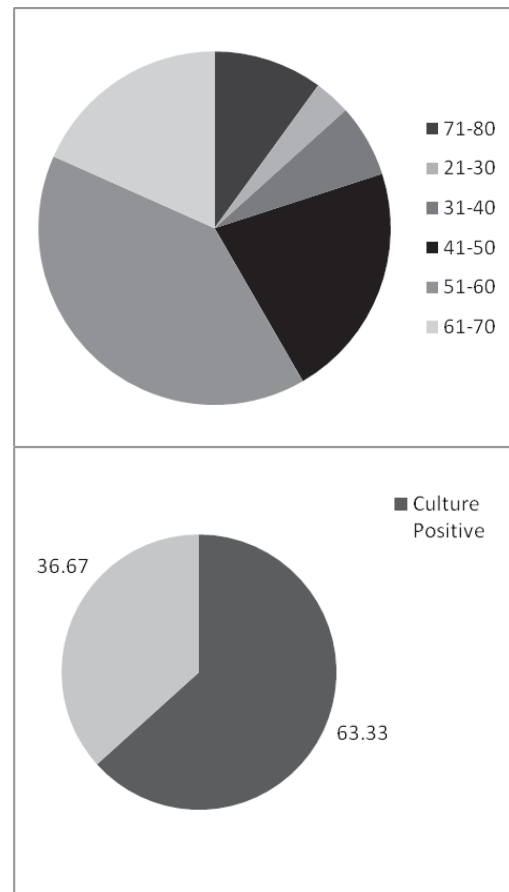
(Bio-Vendor, Germany) and the hs-CRP level was measured using an immune-turbidimetric assay (Beckman, Carlsbad, CA 92010, USA).

All data were checked and interpreted after collection and from the primary data tables and graphs were made. Levels of PCT and hs-CRP were expressed as the means ± SD or median ±inter quartile range. A p-value of <0.05 was considered to be statistically significant. A nonparametric Levene's test was used to verify the equality of variance in the samples data. The quantitative variables were analyzed by Mann Whitney U test. Data was applied in the SPSS version 16 for statistical analysis. Their diagnostic utilities were compared using receiver operating characteristic (ROC) curves and the areas under each respective curve were calculated.

The study was approved by the ethics committee of BIRDEM General Hospital. Written informed consent was obtained from all patients and their guardians.

**Results:**

Total of 60 patients were included in this study with at least 2 SIRS criteria and their mean age was 51.90±9.89 years. Age-matched patients of both sexes were enrolled for this study where male 51.2% and female 48.8% and 50-60 years age group was the commonest 40%. Figure-1 shows patient's age distribution and bacteriological culture pattern.



**Figure-1**

Inflammatory response syndrome may appear in non-inflammatory conditions and without bacterial infection also. The gold standard method to prove sepsis is positive bacteriological culture. In this study 38 (63.33%) patients were bacteriological culture-positive and 22 (36.67%) patients were bacteriological culture-negative (Figure-1). In culture, the most common organism was Klebsiella (28.95%) followed by Escherichia coli, Acinetobacter, Pseudomonas aeruginosa, Enterococcus, Extended-spectrum beta-lactamases (ESBL) and Staphylococcus aureus. To see significance of serum PCT and CRP values in bacteriological culture positive and negative patients a nonparametric Levene's test was used to verify the equality of variance in the samples data ( $p < 0.05$ ) which confirmed the non-homogeneity of the distribution because sample data were not normally distributed (Figure-2). Figure 2 shows frequency distribution PCT and hs-CRP values in patients.

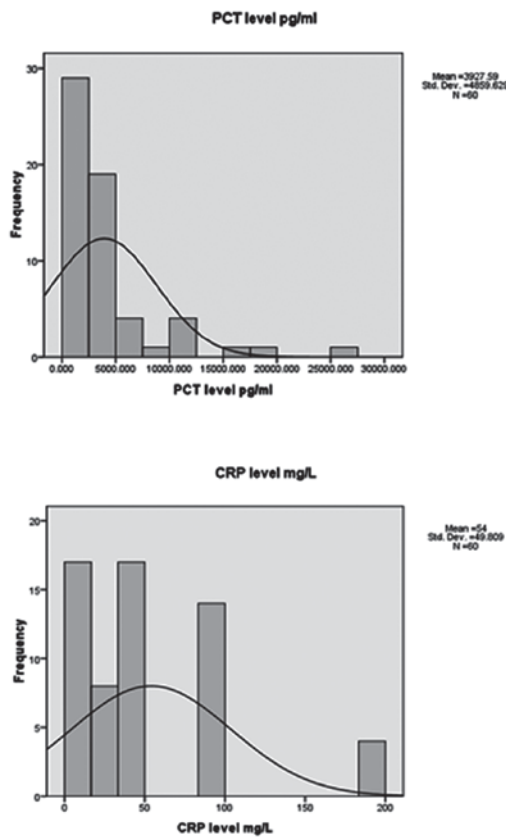


Figure-2

Because of no homogeneity, a nonparametric Mann-Whitney U test was used to see the difference between bacteriological culture positive and negative groups. Statistically, significant difference was found in PCT values in the bacteriological culture positive and negative group, but there was no significant difference found in hs-CRP values. Table 1 shows significance of serum PCT and hs-CRP values to evaluate culture positive and negative patients

Table-1

Biomarkers	Group	Median	Interquartile range	U	Z	P
PCT level pg/ml	Positive	3703.65	3195.69	180	-3.65	0.000
	Negative	688.08	2219.11			
hs-CRP level mg/L	Positive	48	84	394.50	-.369	0.712
	Negative	48	39			

We also categorized sepsis into sepsis, severe sepsis, septic shock and multiple organ dysfunctions (MODS)<sup>12</sup>. There was an increasing trend of serum PCT with the developing stages of sepsis. Median and interquartile ranges of values for PCT was (SIRS 208.5±1632.55, Sepsis 2347.07±3244.73, Severe sepsis 2810.4±3449.33, Septic shock 4162.33±6148.215, MODS 5262.3±4606.41) respectively. But CRP did not show any gradual increasing trend with the progression of sepsis. Figure 3 shows relation of PCT level with developing stages of sepsis.

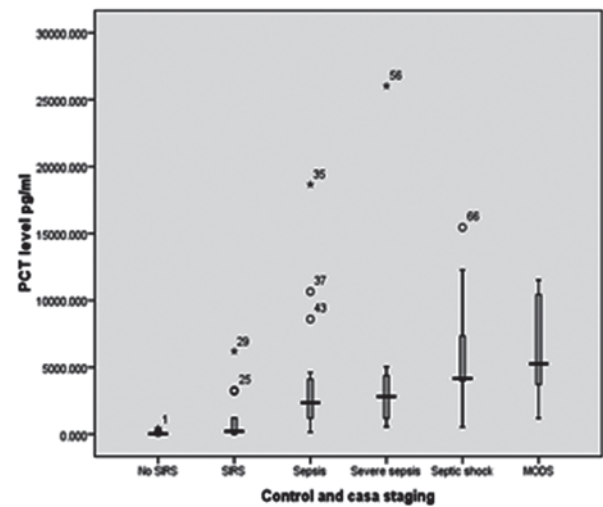


Figure-3

We also determined the performance of serum PCT and CRP as a diagnostic test to evaluate sepsis or bacterial infection compared to the bacteriological culture reports. Receiver operating characteristics (ROC) curve PCT and CRP were made according to the sensitivity and specificity of serum values of these markers using data from all study subjects. Area under the curve (AUC) for PCT was 0.785(95%CI, 0.654-0.915), sensitivity 89.47%, specificity 50%, positive predictive value (PPV) 75.55% and negative predictive value (NPV) 73.33% with the cutoff value of >753pg/ml. AUC for CRP was 0.528(95% CI, 0.378-0.679), sensitivity 68.42%, specificity 77.27%, PPV 83.87% and NPV 58.62% with the cutoff value of >12mg/l. Figure-4 shows ROC showing AUC of PCT and hs-CRP.

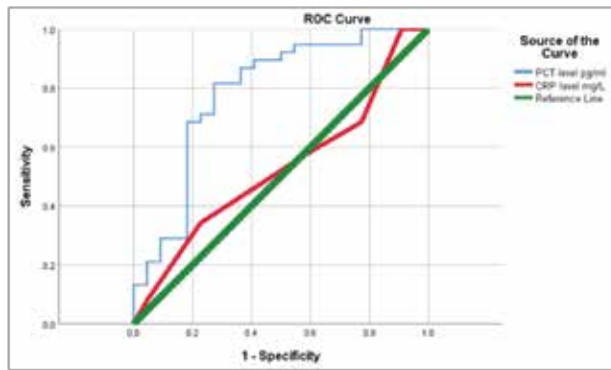


Figure-4

### Discussion:

Sepsis in diabetic patients are major causes of morbidity and mortality worldwide<sup>6</sup>. In 2017, almost 50 million incident cases of sepsis were estimated worldwide and 11 million sepsis-related deaths were reported, representing nearly 20% of all global deaths<sup>13</sup>. Evidence indicates that diabetic patients have an increased risk of infection and several features associated with diabetes influence host response to infection<sup>14</sup>. The researcher found that a higher risk of sepsis compared to the age-matched non-diabetic people and sepsis-related morbidity and mortality compared to non-diabetic individuals were also higher<sup>15</sup>. Diabetic patients have higher rates of colonization by resistant pathogens than non-diabetics and that promotes diabetes is an increasingly common co-morbidity among septic patients<sup>16,17</sup>. So rapid diagnosis and timely initiation of effective therapy of sepsis is a daily challenge among diabetic patients. Identification of sepsis has a major impact on the clinical course, management, and outcome of critically ill patients. There is no multicenter-based study in our country to determine the incidence of sepsis in our country. But in a prospective cross-sectional study done in BIRDEM General Hospital ICU, 95 (41%) sepsis patients were isolated within 228 patients<sup>18</sup>. In this study 60 patients with at least 2, SIRS criteria were enrolled and their mean age was 51.90±9.89 years. The commonest age range was between 51 to 60 years and males were 51.2% and females were 48.8%. It's indicated that elderly populations were an at-risk group to develop sepsis and may be more prone to developed sepsis. Inflammation or infection leads to the activation of the inflammatory cascade and various cells can produce a multitude of pro-inflammatory cytokines and acute phase proteins. CRP and PCT can draw statistically significant differences between the sepsis group and the non-sepsis group<sup>19</sup>. Systemic response to infection is known as sepsis and proceeds to severe sepsis, shock and organ dysfunction if untreated, so early diagnosis of sepsis is very important to make an effective decision about the treatment plan. Bacteriological culture is the gold standard method to isolate the infection. But an early diagnosis of sepsis can be difficult because positive bacteriological samples may be late or absent, the clinical interpretation of infections may be

ambiguous, and traditional markers of infection may be nonspecific. So if any biomarker can predict bacterial infection in the earlier phase of sepsis in the patient with an inflammatory response that will help in treatment procedure and minimize progression of diseases. In this study, PCT values are statistically significant to predict bacterial infection and draw a difference between patients with and without sepsis. Luzzani and his colleagues did a prospective study over ICU patients and found PCT is a better marker than CRP to diagnose sepsis<sup>20</sup>. PCT also showed a better and closer correlation than that of CRP with the severity of sepsis and organ dysfunction and the rise in sepsis-related organ failure assessment score was related to a higher median value of PCT<sup>21</sup>. Klaus and his colleagues identify PCT and IL-6 is better than CRP to predict survival rate in patients with severe sepsis<sup>22</sup>. PCT is valuable for the early diagnosis of bloodstream infection and concentration in patients with Gm (-ve) bacterial bloodstream infection was significantly higher than those of Gm (+ve) bacterial bloodstream infection group<sup>23</sup>. A single-center prospective follow-up study proved that PCT superior to CRP in detecting patients with severe sepsis is a significant independent predictor to diagnose sepsis<sup>24</sup>. In this study ROC curve shows AUC for PCT was 0.785 (95% CI; 0.654- 0.915), sensitivity 89.47%, specificity 50%, PPV 75.55% and NPV 73.33% with the best cut-off value >753pg/ml which support PCT as a superior and reliable marker of sepsis. In our study, serum PCT shows an increasing trend with the developing stages of sepsis. PCT starts to rise earlier and returns to normal concentration more rapidly than CRP, allowing for an earlier diagnosis and better monitoring of disease progression which indicates PCT as a better diagnostic and prognostic biomarker of sepsis<sup>25</sup>.

### Conclusion:

It is highly unlikely that a single parameter will ever be able to diagnose sepsis in diabetic patients. Rapid diagnosis and timely initiation of effective therapy mainly depend on appropriate clinical observation along with suitable and useful laboratory tools. The PCT is a unique biomarker having both diagnostic and prognostic value compared to other conventional markers for sepsis. Our results suggest that serum PCT is a more reliable diagnostic marker of sepsis than other traditional markers like hs-CRP in diabetic patients. Combinatorial use of these biomarkers will help in early diagnosis and also greatly improve outcomes. However more prospective, large scale and multicenter-based studies are required to validate the role of PCT in-depth as diagnostic markers of sepsis.

### Grant information

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### Competing interests

No competing interests were disclosed.



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