ORIGINAL ARTICLE

Utility Of Procalcitonin As A Diagnostic And Prognostic Biomarker Of Sepsis In Comparison To Culture & Other Inflammatory Markers

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Abstract

Background
Rapid diagnosis and timely initiation of effective therapy are the major challenges in intensive care units (ICUs) despite the advances in critical care medicine. Procalcitonin (PCT) is an innovative valuable laboratory marker in this regard.

Objectives
This study was undertaken to introduce PCT as a routine tool in regional hospitals by evaluating the utility of PCT in early diagnosis as well as in assessment of severity in septic patients in comparison to the traditional methods and inflammatory markers like cultures and C-reactive Protein (CRP).

Method & Materials
PCT and CRP were simultaneously measured in 73 medico-surgical ICU patients. The results of PCT, CRP and microbiological cultures were compared according to the five categories of PCT concentrations and the American College of Chest Physicians (ACCP) criteria based study groups.

Results
The clinical presentation of 75.3 % cases revealed a range of systemic inflammatory responses (SIRS). The diagnostic accuracy of PCT was higher (75.34%) with greater specificity (72.2 %), sensitivity (76.36%), positive and negative predictive values (89.36 % and 50%), positive likelihood ratio (2.75) as well as the smaller negative likelihood ratio (0.33). Both serum PCT and CRP values in cases with sepsis, severe sepsis and septic shock were significantly higher from that of the cases with SIRS and no SIRS ($p < 0.01$).

Conclusion
The diagnostic utility of both PCT and CRP are close yet PCT is found to be superior to that of CRP or microbiological culture in terms of accuracy in identification of patients with sepsis and to assess the severity of sepsis as well.

Keywords
Procalcitonin; C-reactive protein; microbiological culture; systemic inflammatory response syndrome (SIRS)

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Introduction

Early diagnosis and appropriate therapy of sepsis is a daily challenge in the emergency room and in intensive care units. Despite the enormous investment in critical care resources, severe sepsis mortality ranges from 28% to 50% or greater. Moreover, cases of severe sepsis are expected to rise in the future for several reasons, including: increased awareness and sensitivity for the diagnosis; increasing numbers of immunocompromised patients; wider use of invasive procedures; more resistant microorganisms; and an aging population.[1] Definitions for the terms of "SIRS", "sepsis", "severe sepsis" or "septic shock" have been proposed by the ACCP/SCCM Consensus Conference in 1992, and are now widely used. Systemic inflammatory response syndrome (SIRS) encompasses a variety of complex findings that result from systemic activation of the innate immune response. The clinical parameters include two or more the following: fever (>380 C) or hypothermia (<360 C), increased heart rate (>90 beats/min), tachypnea (>20 breaths/min) or hyperventilation (PaCO2 <32 mm Hg), and altered white blood cell count (>12,000 cells/mm3 or <4000 cells/mm3) or presence of >10% immature neutrophils. Sepsis is defined as SIRS resulting from infection, whether of bacterial, viral, fungal, or parasitic origin. Severe sepsis is associated with at least one acute organ dysfunction, hypoperfusion, or hypotension. [2,3]

Traditional markers of systemic inflammation, such as CRP, ESR and white blood cell count (WBC), also have proven to be of limited utility in such patients due to their poor sensitivity and specificity for bacterial infection. Moreover, microbiological cultures; the conventional gold standard diagnostic method for sepsis, are often time consuming, do not reflect the host response of systemic inflammation or the onset of organ dysfunction, and sometimes misleading with false positive or false negative reports. These shortcomings in both culture and available be considered at risk of developing severe sepsis or septic shock.[7,8]

Hyperprocalcitoninemia in systemic inflammation or infection occurs within 2 to 4 hours, often reaches peak concentrations in 8 to 24 hours, and persists for as long as the inflammatory process continues. The half-life of PCT is approximately 24 hours; therefore, concentrations normalize fairly quickly with the patient's recovery. In comparison, CRP takes 12 to 24 hours to rise and remains elevated for up to 3 to 7 days. Because PCT concentrations increase earlier and normalize more rapidly than CRP, PCT has the potential advantage of earlier disease diagnosis, as well as better monitoring of disease progression.[9] Moreover, a number of studies have shown that the systematic use of PCT for sepsis diagnosis and monitoring may also have a positive impact on the reduction of antibiotic (AB) treatment, therefore allowing a shorter stay in the ICU and lower costs per case. This will also be beneficial in combating the increase of antibiotic-resistant micro-organisms which is mainly related to the excess use of antibiotics.[10-13] Additionally, researchers found a ≥30% decrease in PCT levels between day 2 and 3 to be an independent predictor of survival in ICU patients.[14]

Thus, Procalcitonin has been identified as a promising biomarker that may provide added value to the clinical decision process, i.e. assist in diagnosis, assess prognosis, and assist in treatment selection and monitoring. This biomarker is now widely used in Europe and recently it was approved by the FDA in USA for the diagnosis and monitoring of sepsis and evaluation of the systemic inflammatory

response in the clinical arena.[15] For the very first time, PCT is now commercially available in our country and is being used as a biomarker at the Apollo Hospital, Dhaka. So far to our knowledge this would be the first study done with PCT on Bangladeshi population. This study was undertaken to detect and to evaluate the level of PCT compared to other conventional methods like CRP, blood culture with an aim of introducing PCT as a routine tool for early diagnosis and treatment of sepsis in our country.

Materials and Methods

This was a single center cross sectional study carried out at the Apollo Hospital, a tertiary care hospital in Dhaka, Bangladesh, receiving patients from affluent to low-middle socioeconomic status emerging from the entire country. This is the first hospital in Bangladesh, accredited by the Joint Commission International Accreditation (JCIA), a subsidiary of the United States based Joint Commission on Accreditation of Healthcare Organizations (JCAHO); serving the community as a high-intensity tertiary care referral center. Out of all the adult patients (> 18 years of age) consecutively admitted to the mixed medico-surgical intensive care unit (ICU) of the hospital during the period of January 2011 to December 2011, 73 cases were finally included in this study. Neurosurgical and elective surgical patients without complications were excluded. The study was approved by the local Ethics Committee and care of the patients was directed by the same existing protocols.At the time of admission and every day thereafter, signs and symptoms, clinical and laboratory data regarding PCT and CRP levels were collected along with other relevant laboratory tests according to the patient's clinical status (BT, WBC count, and arterial blood-gas analysis). The requests for PCT and CRP tests were variable in each patient (once – 12 times). PCT measurement was performed by enzyme-linked fluorescent assay (B.R.A.H.M.S.; Diagnostica AG, Hennigsdorf/Berlin, Germany)[16] and CRP by a nephelometric method (Dadebehring BN prospec 100, Germany). Appropriate samples were collected for microbiological cultures depending on the clinical symptoms.

All the study subjects were categorized into five groups according to the PCT concentrations and the most probable clinical situations provided by the manufacturer[16] (Table I). The study subjects were also grouped according to their clinical, laboratory and bacteriological findings. According to American College of Chest Physicians/Society of Critical Care Medicine criteria2 the patients were split into four groups and studied till recovery (Table II); medicosurgical patients without trauma or SIRS were included into the 'no SIRS' group.

Table I: Grouping of the study subjects according to the serum PCT concentrations.

Study Groups	Serum PCT levels (ng/ml)	Most probable interpretations
Group I	< 0.05	Healthy (no SIRS)
Group II	0.05 – < 0.5	Minor SIRS/local infection
Group III	0.5 – < 2	Moderate SIRS/sepsis
Group IV	2 – < 10	Severe SIRS /sepsis
Group V	≥ 10	Important SIRS due to severe sepsis/septic shock

SIRS: Systemic Inflammatory Response Syndrome

Table II: SIRS and Sepsis Definition (ACCP/SCCM-criteria) 2

SIRS (Systemic Inflammatory Response Syndrome)	2 or more of the following criteria: • Temperature > 38 °C or 36 °C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or PaCO 2 < 32 torr (< 4.3 kPa) • WBC > 12000 cells/mm 3, < 4000 cells/mm3, or > 10% immature (band) forms
Sepsis	Documented infection together with 2 or more SIRS criteria
Severe Sepsis	Sepsis associated with organ dysfunction, including, but not limited to, lactic acidosis, oliguria, hypoxemia, coagulation disorders, or an acute alteration in mental status
Septic Shock	Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time when perfusion abnormalities are detected.

All data was checked and edited after collection. From the primary data obtained, tables were made and interpreted. Results were compared according to the five categories of PCT concentrations as well as the clinical presentation. Data are presented as incidence (%) or mean ± SD. Data was applied in the SPSS version 12 for statistical analysis. Their diagnostic utilities were compared using ROC curves.

Results and Observations

This study included a total of 73 cases; 46 (63%) males and 27 (37%) females. Average age was 28.8 ± 9.3 years. A total of 39 (53.4%) different culture positive isolates were found from 73 clinical specimens. Table III shows the distribution of culture positive isolates of this study. The clinical specimens used for microbiological culture were blood (45.2%), urine (17.8%), wound swab (10.9 %), pus (5.4%), ulcer exudates (6.8 %) and tracheal aspirates (4.1%). The major isolate was Escherischia coli (35.8%). Mixed infection was found in 7 (9.5%), in which Pseudomonas, Acinetobacter and other microorganisms were more common.

Table III : Distribution of culture positive isolates of this study.

Name of the isolates	No.(%)
Escherischia coli	14 (35.8)
Klebsiella spp	7 (17.9)
Pseudomonas aeruginosa	6 (15.3)
Acinetobacter spp	4 (10.2)
Staphylococcus aureus (MRSA)*	5 (12.8)
Candida albicans	3 (7.6)
Total	39 (100)

***Methicillin-resistant Staphylococcus aureus (MRSA)**

The mean PCT was 9.19 ± 13.9 ng/ml (range: 0.03 to 60 ng/ml); and CRP 31.4 ± 19.6 mg/l (range: 0.11 to 63 mg/l). The average PCT and CRP in culture positive patients was 10.9 ± 14.6 ng/ml and 34.2 ± 17.8 mg/l and in culture negative patients the value was 7.1 ± 12.8 ng/ml and 28.2 ± 21.3 mg/l, ($p>0.05$) respectively. Table-IV shows the distribution of the study subjects according to the five categories of PCT and culture results.

Table-IV: Distribution of the study subjects according to the five categories of PCT and culture results.

Groups of PCT	Culture		Total
	Negative	Positive	
Group I	6 (17.6%)	6 (15.4%)	12 (16.4%)
Group II	8 (23.5%)	6 (15.4%)	14 (19.2%)
Group III	6 (17.6%)	7 (17.9%)	13 (17.8%)
Group IV	7 (20.6%)	9 (23.1%)	16 (21.9%)
Group V	7 (20.6%)	11 (28.2%)	18 (24.7%)
Total	34 (46.6%)	39 (53.4%)	73 (100%)

[Analyzed by Chi-square test; $\chi 2 = 1.164$; $p = 0.884$; $df = 4$]

According to the clinical presentation of the patient's only 18 (24.7%) patients were found to have no signs of SIRS. The rest of the cases (75.3 %) presented with a range of systemic inflammatory responses (Figure-1).

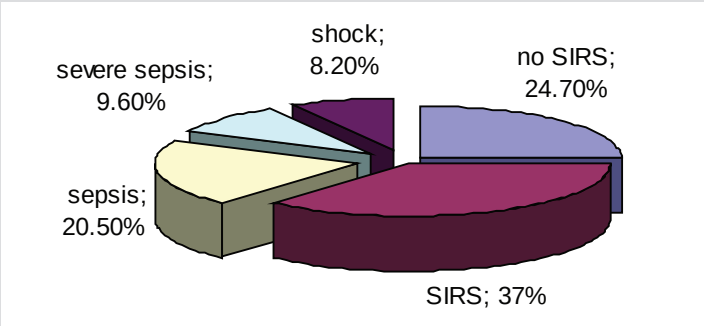

Figure 1: Distribution of the study subjects according to their clinical presentation

For compatible presentation of the distribution of cases according to PCT categories, the study subjects were analyzed as 'no SIRS' and 'SIRS' with positive sepsis to septic shock groups. This analysis showed no statistically significant difference of PCT categories among the 'no SIRS' and 'SIRS ' groups (Figure 2), but the level of significant difference was found to be < 0.01 when the PCT categories were summarized/recoded as no/local infection (group1and 2) and moderate to severe outcome including group 3,4 and 5 (Table-V).

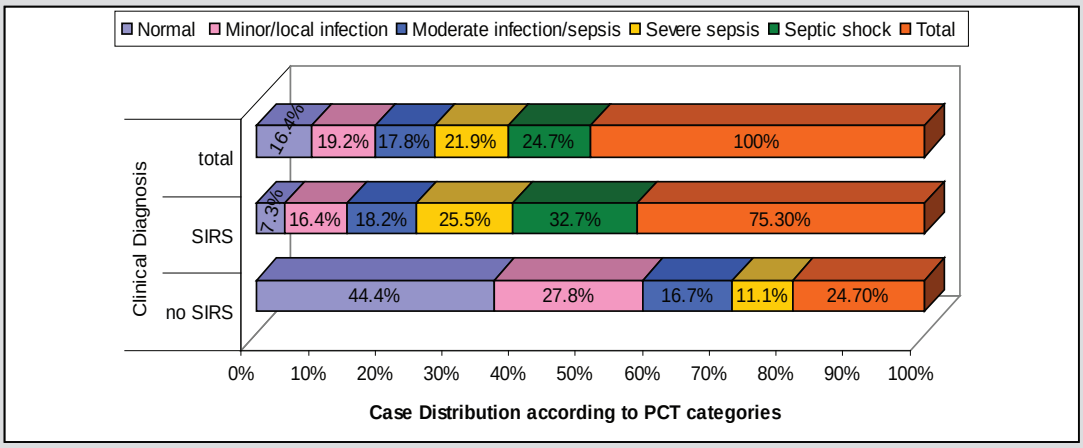

Figure 2: Distribution of the study subjects according to their clinical diagnosis and PCT levels.

Table-V: Distribution of cases according to the interpretation of PCT values and the groups of clinical diagnosis

Interpretation of PCT values		Grouping according to clinical diagnosis		Total
		no SIRS	SIRS to shock	
no/local infection	Number of cases	13	13	26
	% within Grouping according to clinical diagnosis	72.2%	23.6%	35.6%
moderate to severe SIRS	Number of cases	5	42	47
	% within Grouping according to clinical diagnosis	27.8%	76.4%	64.4%
Total	Number of cases	18	55	73
	% of Total	24.7%	75.3%	100.0%

[Analyzed by Chi-square test; $\chi 2 = 11.922$; $p = 0.001$; $df = 1$]

The mean serum PCT and CRP concentrations in the clinically diagnosed groups of the study subjects demonstrated highly significant difference among the groups (Table-VIa). In multiple comparison tests (Games-Howell test) both serum PCT and CRP showed significant raise of the mean values along with increased severity of the clinical presentations in the study subjects (Table-VIb). The mean PCT values in cases with

sepsis, severe sepsis and septic shock were significantly higher from that of the cases with SIRS and no SIRS ($p< 0.01$). Similar finding was observed in CRP concentration among the mentioned groups; however the level of signifi cance was statistically higher (0.001) for severe sepsis versus SIRS and no SIRS groups. There was no significant difference of mean serum PCT and CRP values between the cases with or without SIRS or between severe sepsis group versus patients with sepsis and septic shock ($p>0.05$).

Group by clinical diagnosis	Number of cases (%)	Serum PCT in ng/ml (Mean ± SD)	Serum CRP in mg/l (Mean ± SD)
no SIRS	18 (24.7%)	0.8 ± 1.90	20.2 ± 20.03
SIRS	27 (37.0%)	1.7 ± 2.57	24.9 ± 19.93
Sepsis	15 (20.5%)	11.9 ± 8.82	41.6 ± 8.90
Severe sepsis	7 (9.6%)	26.2 ± 9.99	48.0 ± 6.92
Septic shock	6 (8.2%)	40.8 ± 14.83	49.5 ± 9.15
Total	73	9.1 ± 13.90	31.4 ± 19.65

($p<0.001$ by ANOVA)

Table-VIb: Multiple comparisons of serum PCT and CRP concentrations between the clinical groups of the study subjects.

Group by clinical diagnosis		P-values for PCT	P-values for CRP
no SIRS *vs*	SIRS	0.703	0.937
	sepsis	0.002(¶)	0.004 (¶)
	severe sepsis	0.003(¶)	0.000(†)
	shock	0.006(¶)	0.001(¶)
SIRS *vs*	no SIRS	0.703	0.937
	sepsis	0.004(¶)	0.005(¶)
	severe sepsis	0.003(¶)	0.000(†)
	shock	0.007(¶)	0.002(¶)
Sepsis *vs*	severe sepsis	0.050	0.400
	shock	0.020(*)	0.436
Severe sepsis *vs*	shock	0.325	0.997

(*): The mean difference is significant at the 0.05 level; (¶): at the 0.01 level, and (†): at the level 0.001. The patients with PCT level > 10 ng/ml revealed mortality rate of 16.6%; the remainder of the patients showed adequate evolution with a tendency of getting better. The average hospital stay was 8.2 days.

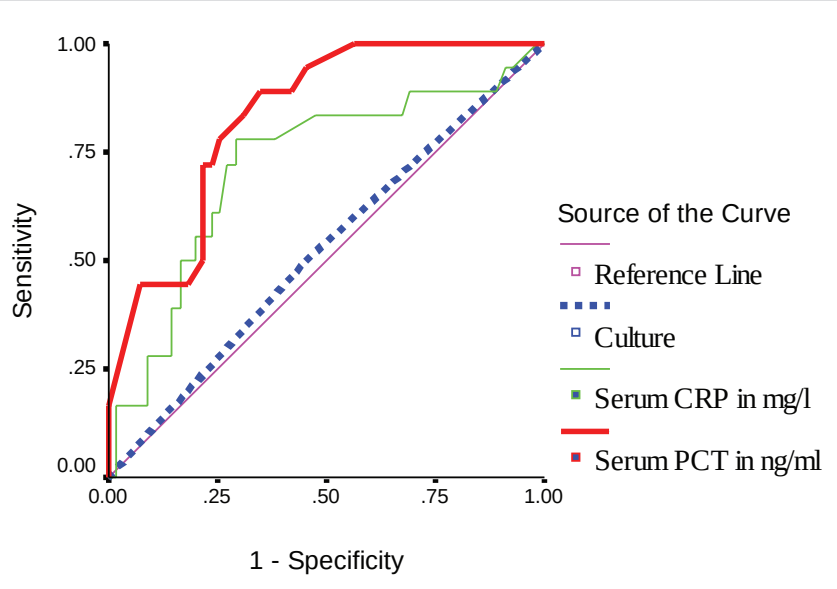

Figure 3: Relative operating characteristic (ROC) curves of PCT, CRP and microbiological culture results.

The area under the ROC curve (AUC) for PCT was 0.830 (95% confidence interval: 0.73 – 0.92), for CRP 0.718 (95% confidence interval: 0.57 – 0.86) and for culture 0.532 (95% confidence interval: 0.36 – 0.67); shown in the figure 3. The difference between the AUCs for PCT and culture results was statistically significant with area difference of 0.307 (p=0.001). However, no significant difference was observed between the AUCs for CRP and PCT or culture. In this study, the optimum statistical cut-off value for PCT and CRP were 0.3 ng/ml (sensitivity: 77 %; specificity: 78.2 %) and 6.8 mg/l (sensitivity: 33 %; specificity: 85.5 %), respectively.

Table VII: comparison of the validity tests of PCT, CRP and microbiological cultures in the diagnosis of high to any possibilities of sepsis (overall).

Validity tests	High to any possibilities of sepsis		
	PCT	CRP	Culture
Sensitivity	76.36% (62.98%-86.7%)	85.45% (73.3%-93.5%)	54.5% (40.5% - 68.03%)
Specificity	72.2 %(46.52%-90.31%)	33.3% (13.34%-59%)	50 % (26.02% - 73.98%)
(+)ve LR	2.75(1.29-5.87)	1.28 (0.91- 1.81)	1.09 (0.65-1.84)
(-)ve LR	0.33 (0.19-0.57)	0.44 (0.17 – 1.09)	0.91 (0.53-1.57)
PPV	89.36 %(76.9%-96.45%)	79.66 %(67.1%-89%)	76.92% (60.67% - 88.87%)
NPV	50% (29.93%-70.07%)	42.86% (17.6%-71.1%)	26.47% (12.88%-44.36%)
Accuracy	75.34%	72.6%	53.42%

(+)ve LR: Positive Likelihood Ratio; (-)ve LR: Negative Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

As shown in Table VII, the sensitivity of CRP was the highest of all. However, PCT shows the highest level of accuracy (75.34%) with greater specificity, positive and negative predictive values, positive likelihood ratio as well as the smaller negative likelihood ratio. Microbiological culture results reveal 53.42% accuracy with higher specificity (50 %) than CRP.

Discussion

PCT was first described as a marker of the extent and course of systemic inflammatory response to bacterial and fungal infections in 1993 by Assicot.[13] Ever since then Procalcitonin (PCT) has been examined extensively as a marker for systemic inflammation, infection, and sepsis, both singularly and in combination with other markers such as CRP, in adults and children in ICU setup. The predominant assay used in most studies has been an immunoluminometric assay, called the LUMI test, manufactured by Brahms. In recent years immunofluorescent assays were given preference. The only study reported in our country earlier was conducted on neonatal sepsis using a rapid semi quantitative immunochromatographic method.[17] The quantitative immunofluorescent assay is being practiced for the first time in this study.

In this study, cultures were positive in 53.4% of microbiological culture specimens (n = 39); E. coli being the major (35.8%) isolate followed by Klebsiella, Pseudomonas and Acinetobacter. This was in accordance with the reports of Karlsson et al[18] and Andreola et al[19] though the rate of positive culture was less than ours. Karlsson et al18 also reported of significantly higher PCT levels in positive culture cases compared to that of the negative ones. In our observation, both PCT and CRP levels were higher in cases with positive cultures though statistically insignificant (P >0.05). In another Korean study the higher CRP levels associated with positive cultures showed greater statistical significance (P <0.001) than PCT levels (P <0.05).[20] In this study the observation was persistent when the rate of positive versus negative cultures were compared in each PCT groups.

In the present study, plasma levels of PCT and CRP in patients with and without infection at different levels of SIRS were assessed. Patients with moderate to severe sepsis had higher PCT concentrations than patients with no/local infections (P < 0.01). The most recent studies with such reports are given by López et al[21], Ruiz-Alvarez et al[22], and Endo et al.[23]

Both serum PCT and CRP showed significant raise of the mean values along with increased severity of the clinical presentations in the study subjects. Significantly higher mean PCT and CRP values were observed in sepsis, severe sepsis and septic shock cases compared to SIRS and no SIRS when compared at the various severities of systemic inflammation and sepsis. However, a number of studies having not been able to demonstrate significant relations of PCT or CRP with severity raised controversies regarding their utility as prognostic markers.[24] In this study the mortality was confined to the cases with PCT level of > 10 ng/ml even though the rate of mortality was low (16.6%).[21]

With regards to the diagnostic performance of PCT, various international literatures found PCT to be a useful marker in the diagnosis of a septic process with a sensitivity of 78 % and a specificity of 94% comparing these values with CRP.[25,27,29] These studies have a more precise methodology towards the desired objectives and the sample number is much greater for which the statistical significance was much better. In this study PCT showed highest level of accuracy (75.34%) with greater specificity (72.2%),

positive and negative predictive values, positive likelihood ratio as well as the smaller negative likelihood ratio. However, sensitivity of CRP in the diagnosis of sepsis was found to be higher (85.45%) than PCT (76.36%). Furthermore, the AUC for infection identification was greater for PCT, followed by CRP and microbiological cultures. These data agree with the recently reported articles.[25-27] By convention, marked changes in prior disease probability can be assumed in PLR exceeding 10.0 and NLR below 0.1.28 Procalcitonin had a higher PLR and lower NLR than did CRP and complement proteins. These results are in agreement with those of Clec'h et al29, Ruiz-Alvarez et al.[22] and others.[25,27]

Few studies have reported of lower diagnostic performance of PCT than CRP in differentiating between sepsis and SIRS.[30,32] In contrast to this, majority of studies have reported that procalcitonin was a better marker to estimate the severity, prognosis, or further course of the sepsis.[33,36] This study was consistent to the others with a few minor limitations. First, serial PCT monitoring every day was avoided which may improve its performance as an aid for follow up of sepsis. Second, antimicrobial therapy may have an impact on PCT values which could not be explained with our study design.

Conclusion:

Rapid identification of infection has a major impact on the clinical course, management, and outcome of critically ill intensive care unit (ICU) patients. Procalcitonin represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock, difficult diagnoses in critically ill patients. Procalcitonin is superior to C-reactive protein. Procalcitonin should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units in our country. However, further large scale studies are recommended to evaluate the diagnostic as well as prognostic utility of PCT in ICU setting of tertiary care hospitals in Bangladesh.

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