http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i3.110

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Serum Procalcitonin: A Suggestive Predictor for Sepsis among Critically Ill Patients at S.M.S. Hospital, Jaipur

Authors
Dr Sarita Netra, Dr Rameshwari Bithu
Department of Microbiology, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, Rajasthan, India
*Corresponding Author
Dr Sarita Netra
Department of Microbiology, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, Rajasthan, India

Abstract
Background: *Despite improvements in the understanding of pathophysiology and new treatment options for sepsis, the mortality rate continues to be elevated. It is often difficult to distinguish critically ill patients with sepsis, organ dysfunction or shock from patients with similar clinical signs and laboratory findings without infections. Procalcitonin (PCT) has been proposed as an effective indicator of infection and as a useful marker of the severity of sepsis. The aim of this study was to evaluate serum PCT in critically ill patients admitted with suspected sepsis.*
Methods: *Prospective study conducted over a period of one year, a total of 150 critically ill patients with suspected sepsis were included. Serum procalcitonin level was assessed on 1st day, 3rd day and 7th day of illness.*
Results: *PCT was positive in 92% of cases, blood culture was positive in 34.67% of cases, statistically significant correlation of PCT with blood culture positivity ($p<0.05$). PCT positivity rate and mean PCT level decreased with time as sepsis got treated. Significantly higher mean PCT in culture positive sepsis and among these in bacterial sepsis. PCT kinetics was found to be of prognostic value from day 3 of sepsis. ROC analysis revealed maximum sensitivity of 98.08% and a specificity of 38.77%, positive predictive value (PPV) 45.94% and negative predictive value (NPV) 91.67% with a PCT value of 0.31 ng/ml.*
Conclusions: *PCT may direct physicians in their clinical decision making and their stepwise approach to the complex management of critically ill patients with sepsis. It has diagnostic as well as prognostic significance. The addition of PCT to the standard work up of critically ill patients with suspected sepsis might assist in avoiding unwanted antibiotic usage in patients who presents with symptoms similar to infective conditions.*
Keywords: *Procalcitonin, blood culture, critically ill, sepsis, PCT cut off.*

Introduction

Sepsis affects millions of people around the world each year; remains one of the most challenging conditions in the intensive care units. The high mortality rate of patients with sepsis is due to its complications, hence the fact that an early

diagnosis and prompt antimicrobial therapy is crucial in the treatment of bacterial sepsis for saving lives. Blood culture is considered the gold standard for detecting pathogens in patients with sepsis, which can isolate and identify the causative agent and subsequently test the antimicrobial sensitivity; but results are not available within 24 hours, it cannot be useful to make early therapeutic decisions. Furthermore, cytokines such as IL-6 and IL-8 have been shown to be associated with sepsis severity and patient outcome, but are not established tools for diagnosis and clinical decision-making[1]. On the other hand, CRP is commonly used for detecting infection that is highly sensitive and convenient for clinical follow-up, but has only limited specificity, so 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[2]. Hematological markers of infection like total and differential leucocyte counts may also be non-specific. Identifying early biomarker of sepsis can aid in the diagnosis and therapeutic management of hospitalized patients. Thus, there is need for clinical tool that distinguish bacterial infections from other inflammatory diseases.

Procalcitonin (PCT) is a recently identified indicator of infection and as a useful marker of the severity of sepsis. Hence, the present study was undertaken to evaluate serum PCT in critically ill patients admitted with suspected sepsis.

Materials and Methods

This was a hospital based observational descriptive study conducted from June 2018 to June 2019 in Department of Microbiology, Sawai Man Singh Medical College and attached Hospitals, Jaipur, Rajasthan. This study was approved by ethics and scientific committee. During the study period 150 critically ill patients with suspected sepsis were included.

Inclusion Criteria: Any patient more than 18 years of age presenting with at least two of the following clinical criteria for sepsis were included in this study-

- Temperature >38 ˚C or <36˚C
- Heart rate more than 90 beats per minute
- Respiratory rate more than 20 per minute
- White blood cell count more than 12,000 or less than 4,000/cumm

Exclusion Criteria: Patients with any of the following condition were excluded from the study-

Any surgery in previous 72 hours
Cardiogenic shock
Cardiac arrest
Major trauma
Severe burns, Pancreatitis

Sample Collection: After obtaining all the information required in the proforma, blood sample was taken from each patient for blood culture and serum procalcitonin (PCT) on admission. Serum procalcitonin level was monitored on 1st day, 3rd day and 7th day of illness. Serum was separated from blood in plain vial by centrifugation at 3000 rpm for 10 minutes.

Serum Procalcitonin Analysis: Serum PCT was assayed by rapid immunochromatographic technique using a commercially available test kit (Elecsys and cobas e 411 analyzers Berlin, Germany). Interpreted as per the manufacturer's recommendations:

i. PCT >10 ng/ml: Severe bacterial sepsis or septic shock
ii. PCT 2 to 10 ng/ml: Severe systemic inflammatory response, most likely due to sepsis unless other causes are known
iii. PCT 0.5 to 2 ng/ml: A systemic infection cannot be excluded
iv. PCT <0.5 ng/ml: Local bacterial infection possible; sepsis unlikely

Blood Culture: Blood culture bottles were incubated at 37°C aerobically. After 48 hours of incubation, examined for indicators of growth. If any of these were present subculture was done on

to Blood agar, MacConkey agar and Chocolate agar. The chocolate agar plates were kept in a candle jar along with a burning candle and sealed. If indicators of growth were not present primary subculture was done after 48 hours of incubation. If no growth occurred on plates after overnight incubation, bottles were incubated further & observed daily for indicators of growth till 7 days. A final subculture was done at the end of day 7 or at appearance of indicators of growth whichever was earlier. If growth occurred on plates, the colonies grown were identified by conventional methods according to the standard laboratory procedure.

Statistical Analysis: After compilation of data statistical analysis was done using SPSS version 17.0 software and P- value <0.05 was considered significant.

Results

In this study out of 150 cases, females (54%) were affected more with sepsis compared to males (46%). Mean age of study population was 47.97 ± 18.55 years and median age was 46.5 years.

PCT was positive (>0.5ng/ml) in 138 (92%) cases, blood culture was positive in 52 (34.67%) cases.

Out of 52 cases with culture positive sepsis, 2 cases (3.85%) had fungal sepsis, 10 patients (19.23%) had gram positive sepsis and 40 patients (76.92%) had gram negative sepsis. Among gram positive organism, the most common pathogen was *Enterococcus* spp. and among gram negative organism, the most common pathogen was *Enterobacter aerogenes*.

There was statistically significant correlation of PCT value with blood culture positivity rate ($p<0.05$) (Table 1).

On day 1 and 3 of sepsis, out of 150 cases, PCT was positive in 92% and 73.33% of cases respectively, while on day 7 of sepsis, out of 143 cases (7 patients expired before 7th day of illness), it was positive in only 27.27% of cases, hence it's positivity rate decreased with time. PCT positivity rate and mean PCT level decreased with time as sepsis got controlled after instituting the antimicrobial therapy. This difference in mean PCT levels on day 1, day 3 and day 7 of sepsis was statistically significant ($p<0.05$) (Table 2).

Difference in mean PCT value among culture positive and culture negative sepsis on day 1 of sepsis was statistically significant, while on day 3 and day 7 of sepsis this difference was not statistically significant (Table 3).

Mean PCT values were significantly higher in patients with bacterial sepsis than in patients with fungal sepsis (Table 4) and in patients with gram negative sepsis than in patients with gram positive sepsis (Table 5).

Total 14 patients died of sepsis; there was no significant difference in mortality rate among different levels of PCT (Table 6).

Mean PCT level among survivors gradually decreased after instituting antibiotic therapy, while it remained elevated in non survivors. Difference of mean PCT level on day 1 of sepsis among survivor and non survivor was not statistically significant ($p>0.05$), while this difference on day 3 and day 7 of sepsis was statistically significant (Table 7).

Mean PCT values were higher in geriatric patients but there was no statistically significant difference in mean PCT level among different age group of patients ($p>0.05$).

Though mean PCT was higher in female patients (mean PCT 15.86 ± 18.97ng/ml) in comparison to males (mean PCT 12.15±14.87 ng/ml) but this difference was not statistically significant, there was no correlation of PCT with gender ($p>0.05$).

To estimate the diagnostic performance of PCT, cut-off value of 0.31 ng/ml and AUC = 0.685 (95% CI = 0.595–0.775) was found significant ($P<0.05$) to differentiate culture positive sepsis from culture negative sepsis with sensitivity 98.08%, specificity 38.77%, positive predictive value (PPV) 45.94% and negative predictive value (NPV) 91.67%.

Table 1: Blood culture results of study population with different levels of PCT

	No. of patients (%)	**No. of Blood culture positive patients (%)**	**Organism grown (No. of cases)**
<0.5 ng/ml	12 (8%)	1 (8.33%)	*Streptococcus* spp(1)
0.5 to 1.9 ng/ml	22 (14.67%)	4 (18.18%)	*CPS* (1) *Enterococcus* spp (2) *Klebsiella* spp (1)
2 to 10 ng/ml	53 (35.33%)	16 (30.19%)	*Acinatobacter* spp (1) *CPS* (1) *E. coli* (2) *Enterobacter aerogenes*(6) *Enterobacter cloacae* (2) *Enterococcus* spp (2) *Candida* spp (2)
>10 ng/ml	63 (42%)	31 (49.21%)	*Acinatobacter* spp (5) *CPS* (1) *E. coli* (5) *Enterobacter aerogenes*(3) *Enterobacter cloacae* (4) *Enterococcus* spp (2) *Klebsiella* spp (4) *Proteus mirabilis* (1) *Pseudomonas aeruginosa* (6)
P value		<0.05	

Table 2: Comparison of PCT levels on Day 1, Day 3 and Day 7 of sepsis

Day of sepsis	**PCT positive No. (%)**	**PCT negative No. (%)**	**PCT Mean ±SD (ng/ml)**	**Total**	**P value**
Day 1	138 (92%)	12 (8%)	14.15±17.25	150 (100%)	<0.05
Day 3	110 (73.33%)	40 (26.67%)	5.13±9.29	150 (100%)	
Day 7	39 (27.27%)	104 (72.73%)	2.95±12.79	143 (100%)	

Table 3: Comparison of PCT on different days among culture positive and culture negative sepsis

Variable		**Culture positive**	**Culture negative**	**P value**
PCT Mean ±SD (ng/ml)	Day 1	18.36±17.51	11.93±16.78	<0.05
	Day 3	6.19±8.01	4.57±9.89	>0.05
	Day 7	3.01±14.28	2.92±11.95	>0.05

Table 4: Comparison of PCT level among bacterial sepsis and fungal sepsis

	PCT positive No. (%)	**PCT negative No. (%)**	**Total**	**PCT Mean ±SD (ng/ml)**	**P value**
Bacterial sepsis	49 (98%)	1 (2%)	50 (100%)	18.91±17.63	<0.05
Fungal sepsis	2 (100%)	0 (0%)	2 (100%)	4.63±2.14	

Table 5: Comparison of PCT level among gram positive sepsis and gram negative sepsis

	PCT positive No. (%)	**PCT negative No. (%)**	**Total**	**PCT Mean ±SD (ng/ml)**	**P value**
Gram positive sepsis	9 (90%)	1 (10%)	10 (100%)	13.33±25.6	<0.05
Gram negative sepsis	40 (100%)	0 (0%)	40 (100%)	20.3±15.15	

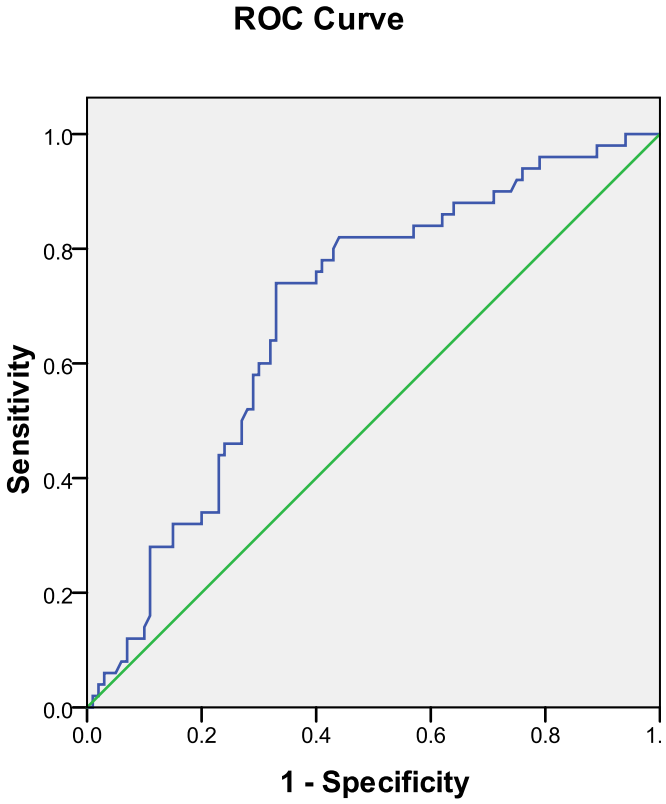
Table 6: Outcome among different levels of PCT

PCT level	Survivor No. (%)	Non survivor No. (%)	Total No. (%)	P value
<0.5 ng/ml	12 (100%)	0 (0%)	12 (100%)	0.21
0.5 to 1.9 ng/ml	19 (86.36%)	3 (13.64%)	22 (100%)	
2 to 10 ng/ml	51 (96.23%)	2 (3.77%)	53 (100%)	
>10 ng/ml	54 (85.71%)	9 (14.29%)	63 (100%)	
Total	136 (90.67%)	14 (9.33%)	150 (100%)	

Table 7: Comparison of mean PCT among survivor and non survivor on different days of sepsis

Outcome of sepsis	Mean ±SD PCT level (ng/ml)		
	Day 1	Day 3	Day 7
Survivor	13.21±16.81	3.53±5.62	0.48±0.93
Non survivor	23.35±19.36	20.69±19.32	29.97±35.14
P value	>0.05	<0.05	<0.05

Chart 1: Receiver Operating Characteristics (ROC) curve to evaluate the ability of PCT in identifying sepsis in critically ill patients



Discussion

Sepsis is a life threatening condition which needs urgent diagnosis and proper management. The early signs and symptoms of sepsis are nonspecific and subtle and might be easily confused with other non-infectious causes. A definitive diagnosis of sepsis can be made only with a positive blood culture. However, it may yield false positive results due to contamination or negative results even with severe infection. Thus there is need for alternative early valid markers of sepsis in critically ill patients.

Nanda SK et al., and Sharma R et al. reported PCT positivity rate as 74.26%, 49.65% and 94% respectively[3,4].

We observed statistically significant correlation of PCT value with blood culture positivity rate ($p<0.05$); higher the serum PCT level, more likelihood of blood culture positivity. A study by Lopez FR et al found that all the patients that presented with positive cultures, had PCT levels > 0.5 mg/dl and the correlation of PCT with culture was significant ($p=0.004$)[5]. Riedel S et al also observed statistically significant differences for PCT levels in relation to blood culture results[6].

We found statistically significant difference in mean PCT value among culture positive and culture negative sepsis on day 1 of sepsis but not on day 3 and day 7 of sepsis. Similarly Riedel S et al. and Yunus I et al. also reported significantly higher mean PCT in patients with positive blood cultures in comparison to patients with negative blood cultures[6,7]. In contrast to our study, Nargis W et al. didn't found significant difference in the average PCT in culture positive patients and in culture negative patients[8].

In our study mean PCT level was significantly higher in bacterial sepsis compared to fungal sepsis. In study by Charles et al. also mean PCT levels was significantly lower in patients with candidemia compared to those with bacteremia[9].

We found significantly higher mean PCT level in patients with gram negative sepsis (mean 20.3±15.15ng/ml) than in patients with gram positive sepsis (mean 13.33±25.6 ng/ml) ($p<0.05$). Mean PCT values in studies by Yunus I et al. and Yan ST et al. were also found to be higher in patients with gram negative as opposed to gram positive infection[7,10]. Nanda SK et al. reported the difference in serum PCT concentrations between Gram-negative and Gram-positive bacterial infections wasn't significant[3].

In present study there was no significant difference in mortality rate among different levels of PCT. Sudhir U et al. didn't find any significant association between the level of serum PCT at presentation and mortality rate in their study[11]. Yunus I et al. also observed that PCT values were not statistically significantly different among various outcomes[7].

Difference of mean PCT level among survivor and non survivor was not statistically significant on day 1 of sepsis, while on day 3 and day 7 of sepsis this difference was statistically significant. Our findings are in line with a prospective study by Lipińska-Gediga M et al., they determined that single serum PCT measurement, regardless of absolute value, has a discriminative impact but no prognostic significance during the first 2 days of therapy[12]. Another study by Azevedo JR et al also showed that the initial concentration of PCT was not significantly different among survivors and non survivors groups, but the differences between the two groups after 24 and 48 hours were statistically significant[13]. Other authors also reported that the course of PCT levels over time, rather than absolute PCT values, affect the prognosis of systemic inflammation; continuously declining PCT levels indicate a better prognosis, even if the peak PCT values are very high. A persistent increase or failure to decline in the PCT levels has been related to higher mortality rate in sepsis. Hence, PCT kinetics, rather than the baseline or the peak values, correlate with patient outcome.

We didn't find statistically significant correlation of PCT with age and gender. Shokouhi B et al. conducted a study to examine the diagnostic and prognostic performances of serum procalcitonin in adult and elderly patients with bloodstream infections; they didn't find statistically significant difference in mean PCT level among adult and elderly groups, as well as among males and females[14]. Similarly Farrokhpour M et al. also didn't find any correlation of PCT level with gender[15].

In this study, cut-off value of 0.31 ng/ml and AUC = 0.685 (95% CI = 0.595–0.775) was found significant to differentiate culture positive sepsis from culture negative sepsis with sensitivity, specificity, positive predictive value and negative predictive value of 98.08%, 38.77%, 45.94% and 91.67% respectively. Mahmoodpoor A et al. reported PCT cut off values of 0.25 ng/ml with 73% sensitivity and 39% specificity to separate

patient with and without sepsis[16]. In a study done by Sinha M et al. PCT assay revealed moderate sensitivity (86%) and high specificity at a cut off 2 ng/ml[17].

Conclusion

PCT may be helpful in the management of sepsis in critical care. First as, a new test to diagnose sepsis on ICU admission, serum PCT offers a high level precision that other tests cannot provide. The test can be performed in lesser time and gives valuable information long before culture results are available.

PCT evaluation seems to be better predictor to differentiate patients with sepsis and patients without sepsis. It may increase diagnostic certainty & improve patient management. Serial monitoring of PCT may predict prognosis well before changes in clinical condition of the patient.

Sources of support in the form of grants- Nil

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