Original Article

DOI: 10.7860/JCDR/2022/60163.17128

Serum Procalcitonin Correlation with Sepsis Severity and Patient Outcomes: An Observational Study

Internal Medicine Section

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ABSTRACT

Introduction: Sepsis is a life-threatening condition of human body. It is caused by improper response of host immune system to various infective conditions. Procalcitonin (PCT) has been a promising biomarker for aiding early diagnosis, risk stratification and treatment in patients with sepsis and septic shock.

Aim: To study correlation of serial serum procalcitonin (day 1, 3 and 7) with severity of sepsis and patient outcomes (in-hospital stay or mortality).

Materials and Methods: The study was a descriptive, observational study conducted at Krishna Institute of Medical Sciences, Secunderabad, Telangana, India, on 100 patients admitted to Medical Intensive Care Unit (MICU), both males and females of age more than 18 years, with sepsis or septic shock, from August 2019 to January 2021. Serum procalcitonin was measured by BRAHMS PCT-Q immunochromatographic assay using a commercially available test kit. Blood, urine and wound cultures were performed to confirm specific infection. The Chi-square test, Fischer's-exact test and Pearson correlation tests were used to calculate association and correlations amongst qualitative data.

Results: Total 100 patients (mean age was 49.9±17.0 years; 62 males and 38 females) were included in the study. A total of 74 patients were observed to be have sepsis and 26 patients had septic shock. Mortality was 36%. There was a positive correlation with Sequential Organ Failure Assessment (SOFA) score on day 1 and 3, but not day 7. PCT was high in 85% of patients on admission (day 1). Higher levels of PCT was observed both in patients with sepsis (82.4%) and septic shock (92.3%), suggesting that it is a good diagnostic marker in these patients. Mean PCT was higher in death patients compared to discharged patients on day 1,3 and 7 (p-value <0.05). Majority of patients (71.8%) with higher PCT on admission stayed in ICU for less than 5 days, whereas over half (53.3%) with normal PCT had a short ICU stay (p-value=0.18).

Conclusion: Procalcitonin is a useful marker for early diagnosis of sepsis and septic shock and also severity of infection on admission to ICU. High procalcitonin also predicts mortality and can be a useful tool for rational use of antibiotics in patients admitted to ICU.

Keywords: Biomarkers, Mortality, Risk stratification, Septic shock, Sequential organ failure assessment score

INTRODUCTION

Sepsis is a life-threatening condition of human body. It is caused by improper response of host immune system to various infective conditions [1]. Timely diagnosis as well as timely management of septic condition with specific antibiotics is very essential during first few hours of the triage [2]. The reckless and non specific uses of antibiotics for every ailment leads to vigorous rise in opportunistic infection as well as resistance, thus increasing chances of more mortality and the healthcare costs [3,4]. Better and timely diagnosis of causative agent and proper antibiotic therapy has a great future in solving this problem [5].

The use of blood biomarkers can help a lot in future to diagnose and improve septic conditions [6]. In order to improve patient care, the biomarkers need to complement clinical signs as well as other tests for diagnosis and prognosis of the patients. Clinical management of critically ill patients with severe infection and sepsis can be improved by shortening the time to diagnostic and treatment decision (i.e., differentiation of bacterial from other etiologies, including viral, fungal and non infectious) [7].

Early diagnosis and prompt antimicrobial therapy is crucial in the treatment of sepsis for saving lives. Sepsis is a Systemic Inflammatory Response Syndrome (SIRS) that affect all organs. Scientific advancements in molecular biology has helped us to identify relevant biomarkers for early diagnosis of sepsis [8]. WBC, C-Reactive Protein (CRP) and Interleukin-1 (IL-1) are the conventional markers used for diagnosis of sepsis. Compared to CRP, Procalcitonin (PCT) has better diagnostic and prognostic value and will clearly distinguish viral and bacterial meningitis [9,10]. Blood culture is considered as the gold standard for the confirmation of bacteraemia and can isolate and identify the causative agent, but there is time delay, therefore a quick testing of a biomarker is extremely useful for early diagnosis of sepsis [11].

Best prognostic information is derived from serial procalcitonin levels. Decreasing levels are found in patients responding to therapy. Increasing level may indicate treatment failure. Drop of PCT to at least 80-90% from its peak values are reasonable threshold for deescalating antibiotic therapy. PCT alone or in combination with other biomarkers would serve as a promising tool for understanding the prediction, cause, diagnosis, progression, regression and outcome of the treatment regimes. Hence, the present study was planned with the aim to study the role of serum PCT and its correlation with severity of sepsis and in-hospital outcomes (in-hospital stay or mortality).

MATERIALS AND METHODS

This descriptive observational study was conducted in Medical Intensive Care Unit, Krishna Institute of Medical Sciences (KIMS), Secunderabad, Telangana, India, from August 2019 to January 2021, among 100 patients.

Sample size calculation: Simple random sampling method was used in the present study subjects after obtaining Ethics Committee approval from KIMS hospitals (Approval no. KIMS/EC/2019/40-06). The sample size was calculated as per formula given by World Health Organisation [12]:

$$N=(Z^2\times\{P(1-P)\})/d^2$$

Where, d=Absolute precision (value<P) (0.124); P=guess of Population (any value <1)=0.625; Z=Z value associated with confidence (2.578) [13]; N=minimum sample size=100.

Inclusion criteria: Patients both male and female with age more than 18 years, admitted with clinical criteria for sepsis and septic shock in medical intensive care unit and gave consent for performing the investigation were included in the study.

Exclusion criteria: Patients with age less than 18 years of age, who could not either afford or not willing to undergo the investigation and are already vigorously treated with antibiotics outside were excluded from the study.

Study Procedure

Demographic data, history, clinical examinations and details of basic investigations was recorded in a prestructured proforma for all included study participants. Serum procalcitonin was measured by immunochromatographic assay using a commercially available test kit and interpreted as per manufacturers recommendations.

i) PCT >10 ng/mL: Severe bacterial sepsis or septic shock.

ii) PCT 2-10 ng/mL: Severe systemic inflammatory response, most likely due to sepsis unless other causes are known.

iii) PCT 0.5-2 ng/mL: A systemic infection cannot be excluded.

iv) PCT <0.5 ng/mL: Local bacterial infection possible; sepsis unlikely.

Blood culture to determine bacteraemia was performed. Culture of wound discharge to know local infection was done. The BRAHMS PCT-Q, an immunochromatographic test for the semi-quantitative detection of procalcitonin, which is used for diagnosing and controlling the treatment of severe, bacterial infection and sepsis [14]. The colour intensity of the band is directly proportional to the PCT concentration of the sample.

STATISTICAL ANALYSIS

Data collected was entered in Microsoft (MS) excel sheet and analysed by using Statistical Package for Social Sciences (SPSS) version 24.0 International Business Management (IBM) United States of America (USA). Qualitative data was expressed in terms of proportions. Quantitative data was expressed in terms of Mean and Standard deviation. Association between two qualitative variables was seen by using Chi-square/Fischer's-exact test. Pearson correlation test was used to find correlations amongst the qualitative variables.

RESULTS

Total of 100 patients were included and analysed. Mean age was 49.9±17.0 years. Majority of the patients were from 51-60 years age group i.e, 24 and majority of the cases were males i.e, 62. A total of 74 patients were in sepsis and 26 were in septic shock. [Table/Fig-1] showed distribution of patients according to their demographic details and clinical diagnosis.

At the time of presentation, the relevant investigations were done. Mean C-Reactive Protein (CRP) was 25.2±16.7 mg/L, mean serum Glutamic Pyruvic Transaminase (SGPT) 131.6±267.5 units/L of serum, mean serum Glutamic-oxaloacetic Transaminase (SGOT) was 180.5±497.6 U/L, mean serum creatinine was 2.3±3.7 mg/dL, mean SOFA score was 2.2±0.4 and stay in Intensive Care Unit (ICU) was 5.2±3.5 days for all included subjects. Positive blood culture was present in 23 cases, urine culture in 24 cases, sputum culture was present in 15 cases [Table/Fig-2]. Majority of the patients i.e., 69 cases required less than five days of ICU stay, 22 stayed in ICU for 6-10 days and remaining nine patients required 11-15 days of ICU admission [Table/Fig-2].

Out of 100 cases of sepsis, 36 deaths occurred and 64 survived. So, the mortality rate in this study was 36% [Table/Fig-3].

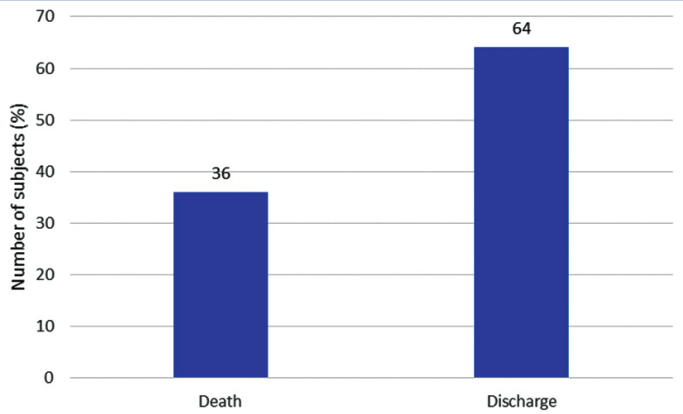
Serum PCT assessment was done on the day 1, on day 3 and day 7. It showed positive correlation between serum PCT at day 1 with SOFA score. Positive correlation was also seen on day 3 but not on day 7 [Table/Fig-4].

Variables		Frequency (n)
Age group (years)	≤20	8
	21-30	8
	31-40	15
	41-50	19
	51-60	24
	61-70	13
	>70	13
Gender	Male	62
	Female	38
Clinical diagnosis	Sepsis	74
	Septic shock	26

[Table/Fig-1]: Demographic details and clinical distribution of all study participants; N=100 patients.

Investigative analysis		Frequency (n)
Blood CS	Positive	23
	Negative	77
Urine CS	Positive	24
	Negative	76
Sputum CS	Positive	15
	Negative	85
ICU stay in days	≤5	69
	6-10	22
	11-15	9

[Table/Fig-2]: Investigative analysis and stay in MICU depicted in the table.
ICU: Intensive care unit; CS: Culture and sensitivity; N=100 patients



[Table/Fig-3]: Bar diagram showing distribution according to outcome; N=100 patients.

SOFA	PCT Day 1	PCT Day 3	PCT Day 7
Pearson Correlation	0.239	0.247	-0.171
p-value	**0.026**	0.055	0.342
Inference	Positive correlation	Positive correlation	Negative correlation

[Table/Fig-4]: Correlation of SOFA with PCT.
p-value <0.05 was considered as statistically significant

Mean PCT at day 1 of admission in death patients was 38.63±31.82 ng/mL and that of discharged patients was 22.58±19.83 ng/mL i.e. statistically significant difference between the PCT values at day 1 of admission was observed (p-value <0.05). Mean PCT on 3rd day of admission in death patients was 39.34±26.31 ng/mL and that of discharged patients was 17.3±20.73 ng/mL i.e. statistically significant difference was seen between the PCT values at 3rd day of admission. Mean PCT on 7th day of admission in death patients was 52.4±33.24 ng/mL and that of discharged patients was 5.67±7.35 ng/mL i.e. statistically significant difference was observed between

the PCT values at 7th day of admission [Table/Fig-5]. This suggests a positive correlation between high PCT values and mortality.

Outcome		N	Serum PCT (Mean±SD) (ng/mL)	t	p-value
PCT at day 1	Death	27	38.63±31.82	2.869	**0.005**
	Discharge	60	22.58±19.83		
PCT at day 3	Death	16	39.34±26.31	3.398	**0.001**
	Discharge	45	17.3±20.73		
PCT at day 7	Death	3	52.4±33.24	6.99	**<0.0001**
	Discharge	30	5.67±7.35		

[Table/Fig-5]: Comparison of mean PCT value according to outcome.
PCT: Precalcitonin; p-value <0.05 was considered as statistically significant

However, when the death rate was compared with respect to high and normal PCT groups, the difference was found to be statistically non significant (p-value=0.89) [Table/Fig-6].

Parameters		High PCT (n=85) (n, %)	Normal PCT (n=15) (n, %)	Test
Outcome	Death (n=36)	31 (36.5%)	5 (33.3%)	χ^2=0.23 p-value=0.89
	Discharge (n=64)	54 (63.5%)	10 (66.7%)	
Diagnosis	Sepsis (n=74)	61 (82.4%)	13 (17.6%)	χ^2=4.66, **p-value=0.043**
	Septic shock (n=26)	24 (92.3%)	2 (7.7%)	
ICU stay in days	≤5 (n=69)	61 (71.8%)	8 (53.3%)	χ^2=3.33 p-value=0.18
	6-10 (n=22)	16 (18.8%)	6 (40.0%)	
	11-15 (n=9)	8 (9.4%)	1 (6.7%)	

[Table/Fig-6]: Distribution of PCT levels with respect to outcome.
p-value <0.05 was considered as statistically significant

There was a positive correlation higher PCT values and diagnosis of sepsis and septic shock and this was found to be to be statistically significant (p-value<0.05). It means both in sepsis and septic shock patients, PCT was significantly elevated. So, PCT is a good and early diagnostic marker of sepsis and septic shock [Table/Fig-6]. Out of 85 cases with high PCT value, 71.8% had ICU stay of less than 5 days as compared to 53.3% cases with normal PCT. Out of 85 cases with high PCT value, 18.8% had ICU stay of 6-10 days as compared to 40 % cases with normal PCT. Out of 85 cases with high PCT value, 9.4 % had ICU stay of 11-15 days as compared to 6.7 % cases with normal PCT. This association was found to be non significant [Table/Fig-6].

DISCUSSION

The previous study of Sinha M et al., included 40 patients from ages ranged 18-84 years with male: female ratio, 2.33:1 [15]. Similarly studies of Martin GS et al., and Todi S et al., reported sepsis to be more prevalent in males [16,17]. Khan AA et al., conducted the study with the objective to assess the diagnostic and prognostic value of PCT in sepsis. Out of total 60 patients, 32 (53.34%) were male and 28 (46.66) were female. A 18 (30%) male and 14 (23.33%) female patients were <50 years of age [13].

The mean PCT in the present study when compared between two groups, it was observed that there was statistically significant difference between the PCT values at day 1, day 3 and day 7. It means PCT was significantly higher in death patients as compared to discharged patients (p-value <0.05). Sinha M. et al., found in his study that one patient amongst 12 patients with PCT greater than 10 ng/mL did not have any signs of sepsis or infection and recovered with inotropic support [15]. Khan AA et al., observed that in 63.33% cases, serum PCT was elevated [13]. They also found significant difference in mortality in patients with raised serum procalcitonin versus normal serum procalcitonin level. The findings are almost consistent with the present study results. This also correlates with the studies by Assicot M et al., and Rey C et al., that serum procalcitonin level is raised in the patients with septicaemia [18,19].

Many previous studies had demonstrated raised serum PCT levels in patients with septic condition and correlated them with the outcome of the disease. PCT can be used for specific diagnosis, and follow-up of ICU patients [20]. Serum PCT levels have been noted to increase with increasing severity of sepsis and indicates that better source control is required [21]. Present study also revealed that every day charting the PCT value is used for monitoring the host response to the infection and the antibiotic treatment.

Biomarkers are expected to provide better information about presence of a relevant bacterial infection, its severity and treatment response, with early and rapid recognition to provide high diagnostic accuracy. PCT as a biomarker fits in many of these criterias and has depicted high diagnostic accuracy for septic condition of the patients [22]. Hence, for assessment of patients with sepsis must include proper use of PCT for early and specific diagnosis and treatment of patients [23]. The present study used immunochromatographic test for the semi-quantitative detection of PCT while most other studies used immunoluminometric method and were able to achieve high sensitivity and modest specificity with a cut-off of 1-1.2 ng/mL [18-21].

Limitation(s)

Small sample size was a limitation for the present study.

CONCLUSION(S)

Higher levels of procalcitonin level had a positive correlation with severity of sepsis on admission to ICU (on day 1 and 3). Higher levels were also seen in most patients with sepsis and septic shock, suggesting that it's a good and early diagnostic biomarker. There was also a positive correlation with mortality in these patients. Measurement of serial procalcitonin values is therefore useful for management decisions in these patients, including rational use of antibiotics. It helps in risk stratification and aggressive line of treatment can be followed in patients with higher procalcitonin, which is predictive of higher severity and higher mortality risk.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 27, 2022
- Manual Googling: Oct 10, 2022
- iThenticate Software: Oct 25, 2022 (23%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 14, 2022**
Date of Peer Review: **Oct 11, 2022**
Date of Acceptance: **Oct 31, 2022**
Date of Publishing: **Nov 01, 2022**