Original Article

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

Internal Medicine Section

SIRISHA JUJJURU[1], GAUTAM PANDURANGA[2], SHIVARAJU KANUGULA[3]

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 (day1, 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 36 females) were included in the study. A total of 74 patients were observed to be have sepsis and 26 patients lhad 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]. 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 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 bacteremia 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: 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.

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).

Inclusion criteria: Patients, both male and female, more than 18 years of age, who were 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.

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 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 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 5 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].

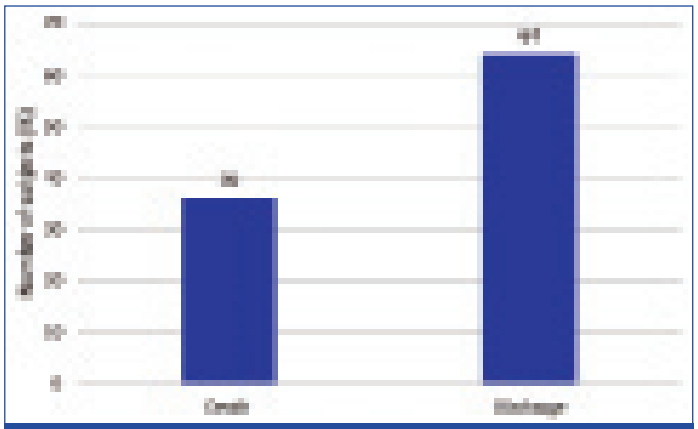
Variables		Frequency (n)
Age group (years)	<20	8
	21-30	8
	31-40	15
	41-50	19
	51-60	24
	61-70	13
	>70	13
Gender	Male	62
	Female	38
Clinical diagnosis	Sepsis	74
	Septic shock	26

[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 to 10	22
	11 to 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

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



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

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].

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 to 10 (n=22)	16 (18.8%)	6 (40.0%)	
	11 to 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 between 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

Sepsis is a life-threatening condition which needs urgent diagnosis and proper management. There is a need for early valid markers of sepsis in critically ill patients. Study included total 100 patients of sepsis fulfilling our eligibility criteria. Majority of the patients were from 51-60 years age (24%). Mean age was 49.9±17.0 years. In the current study, male preponderance was seen with M:F ratio as 1.63:1.

In the present study, serum PCT assay showed higher values (PCT >10 ng/mL) in 85% of sepsis patients on day 1 of admission and in remaining 15% cases it was normal. Mortality was 36%. SOFA score was calculated to indicate the severity of sepsis. There was a positive correlation of PCT with Sequential Organ Failure Assessment (SOFA) score on day 1 and 3, but not day 7. This may be because of improvement in SOFA score by day 7 with antibiotics and other treatments.

When we compared the mean PCT between two groups (death group and discharged group), 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). These findings are similar to the studies done by Sinha M et al., [15], Vaziri M et al., [16] and Khan AA et al., [13].

In the current study, 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. This correlates with the studies by Assicot M et al., that serum procalcitonin level is raised in the patients with septicaemia [17]. According to Ray C et al., procalcitonin was found to be raised in 92.6% [18]. Other studies have also reported rise of procalcitonin in 80-90% cases of sepsis. The present study findings are consistent with the above-mentioned study.

In the present study, 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). This was not statistically significant. Study with a larger sample size and serial PCT measurements would be helpful to clarify the effect of high PCT on length of ICU stay.

Biomarkers should provide a more reliable tool in ascertaining the presence of a relevant bacterial infection, its severity and treatment response. An ideal biomarker should allow, with high diagnostic accuracy, for an early and rapid recognition of sepsis. PCT is a biomarker that fulfills many of these requirements, especially in comparison to other commonly used biomarkers, and that has demonstrated superior diagnostic accuracy for sepsis [19].

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.

REFERENCES

[1] Bracht H, Hafner S, Weiss M. Sepsis Update: Definition and Epidemiology. Anasthesiol Intensiv med Notfallmed Schmerzther. 2019;54(1):10-20.
[2] Rhodes A, Evans LE, Alhazzani W, Mitchell ML, Massimo A, Richard F, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77. 10.1007/s00134-017-4683-6.
[3] Zilahi G, McMahon MA, Povoa P, Loeches IM. Duration of antibiotic therapy in the intensive care unit. J Thorac Dis. 2016;8(12):3774-80.
[4] Jee Y, Carlson J, Rafai E, Musonda K, Huong TTG, Daza P, et al. Antimicrobial resistance: A threat to global health. Lancet Infect Dis. 2018;18(9):939-40.
[5] Fridkin S, Baggs J, Fagan R, Magill S, Pollack LA, Malpeidi P et al. Vital signs: Improving antibiotic use among hospitalized patients. MMWR Morb Mortal Wkly Rep. 2014;63(9):194-200.
[6] Schuetz P, Aujesky D, Muller C, Muller B. Biomarker-guided personalised emergency medicine for all - hope for another hype? Swiss Med Wkly. 2015;145:w14079. Doi: https://doi.org/10.4414/smw.2015.14079
[7] Schuetz P, Raad I, Amin DN. Using procalcitonin-guided algorithms to improve antimicrobial therapy in ICU patients with respiratory infections and sepsis. Curr Opin Crit Care. 2013;19(5):453-60.
[8] Sakr Y, Burgett U, Nacul FE, Reinhart K, Brunkhorst F. Lipopolysaccharide binding protein in a surgical intensive care unit: A marker of sepsis? Crit Care Med. 2008;36(7):2014-22.

[9] Usama MA, Nermin AA, Ayman AAE, Sultan MH. Serum procalcitonin in viral and bacterial meningitis. J Glob Infect Dis. 2011;3(1):14-18.
[10] Hina C, Juhua Z, Yin Z, Mir MA, Franklin M, Prakash SN et al. Role of Cytokines as a Double-edged Sword in Sepsis. In Vivo. 2013;27(6):669-84.
[11] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States. Analysis of incidence, outcome and associated cost of care. Crit Care Med. 2001;29(7):1303-10.
[12] Lwanga SK, Lameshaw S. Sample size determination in health studies. WHO, Geneva,1991. https://apps.who.int/iris/bitstream/handle/10665/40062/9241544058_(p1-p22).pdf;jsessionid=286BF8CD57AA16EBBD38800BF1712FFC?sequence=1.
[13] Khan AA, Singh R, Singh PK. Diagnostic and prognostic significance of procalcitonin in septicemia. Int J Adv Med. 2017;4(3):630-34.
[14] Thermo Scientific B·R·A·H·M·S PCT-Q: Immunochromatographic point-of-care test for the determination of PCT (Procalcitonin) in serum and plasma; https://static.thermoscientific.com/images/D20712~.pdf.
[15] Sinha M, Desai S, Mantri S, Kulkarni A. Procalcitonin as an adjunctive biomarker in sepsis. Indian J Anaesth. 2011;55(3):266-70.
[16] Vaziri M, Ehsanipour F, Pazouki A, Tamannaie Z, Taghavi R, Pishgahroudsari M, Jesmi F, Chaichian S. Evaluation of procalcitonin as a biomarker of diagnosis, severity and postoperative complications in adult patients with acute appendicitis. Medical Journal of the Islamic Republic of Iran. 2014;28:50.
[17] Assicot M, Nylen ES, Jordan MH. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993; 347:518-19.
[18] Rey C, Arcos ML, Coneha A, Mendina A. Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. Intens Care Med. 2007;33(3):477-84.
[19] Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med 2011;171: 1322-31.
[20] Afsar I, Sener AG. Is Procalcitonin a Diagnostic and/or Prognostic Marker in Sepsis? Infectious Diseases in Clinical Practice 2015;23:3-6. Doi: 10.1186/s40560-017-0246-8.
[21] Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. J Antimicrob Chemother. 2011;66 (2):33-40.
[22] Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: A systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011;171(15):1322-31.
[23] Hur M, Kim H, Lee S, Cristofano F, Magrini L, Marino R, et al. Diagnostic and prognostic utilities of multimarkers approach using procalcitonin, B-type natriuretic peptide, and neutrophil gelatinase-associated lipocalin in critically ill patients with suspected sepsis. BMC Infect Dis. 2014;14: 224. Doi: 10.1186/1471-2334-14-224.

PARTICULARS OF CONTRIBUTORS:
1. Resident, Department of Internal Medicine, Krishna Institute of Medical Sciences and Hospitals, Hyderabad, Telangana, India.
2. Associate Professor, Department of General Medicine, Mediciti Institute of Medical Sciences, Hyderabad, Telangana, India.
3. Consultant, Department of Internal Medicine, Krishna Institute of Medical Sciences and Hospitals, Hyderabad, Telangana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Gautam Panduranga,
B115, Mayflower Heights, Mallapur, Hyderabad, Telangana, India.
E-mail: gautampsetty@yahoo.com

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