Role of Serum Procalcitonin as an adjunct biomarker in early diagnosis of sepsis

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Abstract: Background: A very high morbidity and mortality is associated with patients admitted with sepsis. While other biomarkers take some time for confirmation of sepsis, role of serum procalcitonin (PCT) for early diagnosis of sepsis has been explored in recent years. Several studies have widely advocated positively for its use. Current study was carried out to explore common sources of sepsis, determine validity of PCT as a test in determining sepsis and its relationship with sepsis. Materials and Methods: 42 individuals with a probability of sepsis admitted in ICU of a tertiary care hospital in western India were taken as study subjects. Along with necessary microbiological, laboratory and other tests, serum PCT was assessed on admission. PCT values >0.5 ng/ml were considered as positive. Relationship of PCT values was assessed in confirmed cases of sepsis and non-sepsis. Sensitivity, specificity and positive predictive value for PCT were also calculated. Current study was carried out in a private sector. In unavailability of institutional review body, due consents were taken from the stake holders prior to the study. Confidentiality and anonymity of the patients were maintained throughout the periods of study. Results and conclusions: Incidence of sepsis was more in males and people aged 55 years or more. More than half of study subjects were confirmed for sepsis. Respiratory and urinary tract infections were common causes of sepsis. Serum PCT proved to be a good indicator of sepsis in critically ill patients with sensitivity of 82.6%, specificity of 73.3% and positive predictive value of 79.2%. Relationship between PCT and sepsis was statistically significant (Chi-square 11.3 at df 1, $p<0.05$). PCT as an adjunct biomarker can prove helpful in Indian settings for early diagnosis of sepsis. [Mehta M Natl J Integr Res Med, 2020; 11(1):49-53]

Key Words: Serum procalcitonin, early diagnosis of sepsis, biomarkers of sepsis

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Introduction: Sepsis is an increasingly common cause of mortality and morbidity especially in elderly, immunocompromised and critically ill patients[1]. Even when microbiological diagnostics are available, bacteremia is only identified in a proportion of patients who present with sepsis and bloodstream infections[2]. Approximately, 25–35% of patients with severe sepsis and 40–55% of patients with septic shock die within 30 days[3].

Established biomarkers of inflammation like leukocytes, or C-reactive protein can get influenced by non-infectious parameters and may release slowly in order to make the diagnosis delayed. There can always be a role of contamination if bacteriology is positive. Also, negative results do not exclude sepsis. Because of lacking sensitivity and specificity of existing biomarkers, there is a need to look at other markers too which can give an early diagnosis and insight for specific treatment for infectious cause of a generalized inflammatory response[1,3].

Biomarker like Procalcitonin (PCT) has recently gained interest as a possible marker for systemic inflammatory response to infection.PCT is produced by thyroid gland and serum PCT levels are undetectable (<0.1 ng/ml) in healthy humans. During severe infections with systemic manifestations, serum PCT levels may rise above 100 ng/ml which can be of extra-thyroid origin. Even patients with total thyroidectomy can still produce high levels of serum PCT during severe infection. The exact origin of serum PCT during sepsis is uncertain[4].

Several studies abroad have suggested efficacy of PCT as a marker of critical illness. While the Indian literature remains at dearth of such studies, it is imperative that research is carried out in this area in Indian population. Present study was carried out to find out the common sources of sepsis, severe sepsis and septic shock and to evaluate the diagnostic value of serum PCT and its validity as a biomarker for sepsis.

Material And Methods: Study Type, Location And Duration: This observational study was conducted in a tertiary care centre in Vadodara, Gujarat from May 2019 to August 2019.

Inclusion And Exclusion Criteria: 42 patients from the intensive care unit (ICU) with suspected sepsis were included in the study with informed consent and confidentiality of subjects was maintained at all stages of the study. Patients less than 18 years of age and patients with history of malignancy, traumaor recent surgery were

excluded from the study.

Study Design: Confirmation of sepsis was done clinically and by positive blood culture (BacT/Alert system). Patients were identified as having "sepsis syndrome" (sepsis, severe sepsis, septic shock) or no sepsis based on the ACCP (American College of Chest Physicians) recommendations[5].Within 24 hours of admission in the ICU, blood samples were collected from all patients for complete blood count (CBC), prothrombin time (PT),erythrocyte sedimentation rate (ESR), activated partial thromboplastin time, LFT and RFT (liver and kidney function tests), blood culture and serum PCT. Other appropriate and necessary laboratory and radiological investigations were also carried out. Cultures from each patient were sent for confirmation of infection.

Estimation of Serum PCT: Serum PCT was measured by using PCT-Q (B.R.A.H.M.S, Berlin) which is an immunochromatographic test for semi-quantitative detection of serum PCT. With an incubation period of only 30 minutes, the test does not depend on apparatus or calibration[6].

While the PCT value of 0.1 ng/ml is considered to be normal and undetectable for healthy individuals, based on the test sensitivity and specificity provided by the manufacturer, values more than 0.5 ng/ml were considered serum PCT positive.

Statistical Analysis: Validity of PCT assay was calculated in the form of sensitivity, specificity and positive predictive value. Serum PCT cut-off value of ≥0.5 ng/ml was decided. True positives yielded sensitivity (PCT positives/total no. of sepsis cases x 100) while true negatives yielded specificity (PCT positives/total no. of cases without sepsis × 100). Positive predictive value was also calculated. Statistical analysis between PCT positivity and sepsis was carried out using Chi-square test to evaluate the correlation. P value < 0.05 was considered to be statistically significant. Collected data were entered and tabulated in Microsoft excel.

Results: The study included 42 ICU patients with suspected sepsis. Age of patients ranged from 21 to 69 years [male-female ratio, 31:11]. Mean age of the study population was 54.7 years. 26 out of 42 cases (61.9%) were more than 55 years of age.

Majority of the patients with confirmed sepsis were respiratory tract infection cases (64.3% sepsis, 28.6% severe sepsis and 50% septic shock). Urinary tract infections, GIT infections and cellulites were more associated with sepsis while malaria and dengue were more associated with severe sepsis. UTI was responsible for half of the cases of septic shock. [Table 1]

Table 1: Source of Infection in Cases of Sepsis

Source of infection	Sepsis		Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%	No.	%
Respiratory tract	9	64.3%	2	28.6%	1	50.0%	12	52.2%
Urinary tract	3	21.4%	1	14.3%	1	50.0%	5	21.7%
GIT	1	7.1%	0	0.0%	0	0.0%	1	4.3%
Malaria	0	0.0%	1	14.3%	0	0.0%	1	4.3%
Dengue	0	0.0%	2	28.6%	0	0.0%	2	8.7%
Cellulites	1	7.1%	0	0.0%	0	0.0%	1	4.3%
Source not found	0	0.0%	1	14.3%	0	0.0%	1	4.3%
Total	14	100.0%	7	100.0%	2	100.0%	23	100.0%

Table 2: Relationship Between Serum Procalcitonin Levels and Sepsis

PCT values (ng/ml)	Sepsis		No sepsis		Total no. of patients
	No.	%	No.	%	No.
>10	10	90.9%	1	9.1%	11
2 to 10	7	77.8%	2	22.2%	9
0.5 to 2	2	50.0%	2	50.0%	4
<0.5	4	22.2%	14	77.8%	18
Total	23	54.8%	19	45.2%	42

Table 3: Serum Procalcitonin In Sepsis, Severe Sepsis and Septic Shock Patients

PCT values ng/ml	>10		2 to 10		0.5 to 2		<0.5		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
No sepsis	1	9.1%	2	22.2%	2	50.0%	14	77.8%	19	45.2%
Sepsis	6	54.5%	4	44.4%	1	25.0%	3	16.7%	14	33.3%
Severe sepsis	3	27.3%	2	22.2%	1	25.0%	1	5.6%	7	16.7%
Septic shock	1	9.1%	1	11.1%	0	0.0%	0	0.0%	2	4.8%
Total	11	100.0%	9	100.0%	4	100.0%	18	100.0%	42	100.0%

Out of total 42 study subjects, 23 patients (54.8%) were identified as having sepsis (14, 7 and 2 patients respectively classified as having 90.9% of patients with PCT value >10 ng/ml reported sepsis. The proportions of sepsis cases reduced as the PCT levels reduced. 77.8% patients with PCT values between 2 to 10 ng/ml reported sepsis while half of the patients between 0.5 to 2 ng/ml PCT values reported sepsis, severe sepsis or septic shock). 19 patients (45.2%) were not having sepsis. [Table 2]

Relationship between PCT and sepsis was found to be statistically significant. (Chi-square with Yates correction 11.3 at df 1, $p<0.05$) [Table 2] 0.5 ng/ml of PCT was taken as a cut-off and values above that were taken as PCT positive. Sensitivity of PCT as biomarker in sepsis was found to be 82.6% (61.2% to 95.1% at 95% CI) while specificity was 73.7% (48.8% to 90.9% at 95% CI) and Positive Predictive Value was found to be 79.2% (63.6% to 89.2% at 95% CI). [Table 2]

Serum PCT level >10 ng/ml was more associated with sepsis and severe sepsis cases (81.8% cumulatively), while serum PCT level between 2 to 10 ng/ml was more associated with sepsis cases (44.4%). Proportions of sepsis and severe sepsis cases were equal for Serum PCT level 0.5 to 2 ng/ml. 77.8% of no sepsis cases showed PCT levels less than 0.5 ng/ml. Proportions for septic shock were 9.1% and 11.1% respectively for PCT values >10 and 2 to 10 ng/ml. [Table 3]

Discussion: In current study, we explored the possibility of serum PCT as a diagnostic adjunct tool along with clinical findings. It was noted that the incidence of sepsis was more in patients aged over 55 years (61.9%). Age distribution of sepsis cases followed worldly trends. A study from west reported higher incidence of sepsis above 57 years[7].Mean age in an epidemiological study of sepsis in India was 54.9 years in another study[8].

In our study, sepsis cases showed predilection towards males (73.8%). Martin et al in USA and sepsis. The proportion of sepsis patients was less than 1/4th with PCT values less than 0.5 ng/ml which was the cut-off. In nutshell, above the cut-off value of PCT, half or more cases turned out to be of sepsis. [Table 2]

Todi et al in India also found a higher incidence among men in their respective studies[7,8].

Respiratory tract infections (52.2%) were the commonest source of sepsis in our study [Table 1] followed by urinary tract infection. This may be because of higher age groups and imposing risk factors like diabetes amongst them. Calandra et al[9]. Indicated six common infection sites in the causation of sepsis i.e. pneumonia, blood stream infections along with infective endocarditis, intra-abdominal infections, intravascular catheter related sepsis, urosepsis and surgical wound infections. In our study, dengue was found to be primary source of sepsis in two cases (8.7%) while malaria was the underlying cause in one case (4.3%). Majority of literature suggests significant elevation of PCT in bacterial and fungal infections while only a mild elevation of serum PCT in dengue (viral) [10] and malaria (protozoal)[11,12].

Serum PCT has 82.6% sensitivity in the present study [Table 2]. Sudhir U in an Indian study of PCT as biomarker in sepsis found the sensitivity to be 94%.[1] Harbarth et al. in similar study reported sensitivity of 97%.[13] Sensitivity in our study is not as high as other Indian study but it still is a decent number proving utility of PCT as an important biomarker. In our study, specificity of PCT was 73.7% along with positive predictive value being 79.2%. Specificity with a decent positive predictive value is always a good combination to be explored further.

As discussed earlier, serum PCT levels increase during severe generalized bacterial, parasitic or fungal infections with systemic manifestation compared to viral infections. PCT also has longer half-life of 25-30 hours compared to cytokines such as tumour necrosis factor (TNF)-a and interleukin (IL)-6[14].These properties make serum PCT a good indicator of severe generalized infections or sepsis[15,16,17].Localized infections or infections with no systemic manifestation cause a limited rise in serum PCT levels and its utility there is questionable.

PCT secretion begins within 4 hours after stimulation and peaks at 8 hours[18].Major trauma, surgery or cardiopulmonary bypass can yield increased serum PCT levels even in absence of severe infection but the values are not as marked as during severe sepsis and septic shock[19].

Our study does not include surgical cases which can be considered as a study limitation. Another limitation of our study is, serial measurements of PCT on same patients are not taken into account. Also, C-reactive protein (CRP) levels are not compared or taken into analysis. However, most studies have found superiority of PCT in comparison to CRP as a marker of infection and sepsis[15,20].Another limitation of our study can be a relatively smaller sample size but when there is dearth of research in this area especially in Indian settings, our study can prove useful for future research in this area.

PCT as a bio-marker does not replace the importance of good clinical acumen. As an adjunct test on admission in ICU along with CRP and blood culture (at 48 hours), it can help clinicians in early diagnosis of sepsis because the test can be performed within 30 minutes and it gives valuable information long before culture results are available. As a repeat test after 1, 5 and 7 days, it can also help to have some prognostic utility and can provide more antibiotic-free days to the patients (regardless of the outcome of illness i.e. recovery or death). More research in this area can help tweak the antibiotic algorithms too for patients suffering from sepsis.

Conclusion: Incidence of sepsis was higher in patients aged >55 years and in males. 54.8% of all study subjects were confirmed for sepsis. Respiratory tract infection was the most common source of sepsis followed by urinary tract infection. Serum PCT proved to be a good indicator of sepsis in critically ill patients, with sensitivity of 82.6%, specificity of 73.3% and positive predictive value of 79.2%. Relationship between PCT and sepsis was found to be statistically significant. Our results indicate that along with clinical decisions, PCT as an adjunct biomarker can prove helpful in Indian settings for early diagnosis of sepsis and can help curtail related morbidity to a good extent.

References:

1. Sudhir U, Venkatachalaiah RK, Kumar TA, Rao MY, Kempegowda P. Significance of serum procalcitonin in sepsis. Indian J Crit Care Med. 2011;15(1):1–5. doi:10.4103/0972-5229.78214
2. George E. Nelson, VidyaMave, and Amita Gupta, “Biomarkers for Sepsis: A Review with Special Attention to India,” BioMed Research International, vol. 2014, Article ID 264351, 11 pages, 2014. https://doi.org/10.1155/2014/264351
3. Chaudhury A, Rao TV. Bacteraemia in a tertiary care urban hospital in south India. Indian J PatholMicrobiol. 1999; 42:317–20
4. Meisner M. The prognostic value of PCT. In: Meisner M, editor. Procalcitonin (PCT)-A new, innovative infection parameter. Biochemical and clinical aspects. 3rd ed. New York: Thieme Publishers; 2000. pp. 63–8
5. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992; 20:864–74
6. Meisner M, Brunkhorst FM, Reith HB, Schmidt J, Lestin HG, Reinhart K. Clinical experiences with a new semi-quantitative solid phase immunoassay for rapid measurement of procalcitonin. ClinChem Lab Med. 2000; 38:989–95
7. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003; 348:1546–54
8. Todi S, Chatterjee S, Bhattacharyya M. Epidemiology of severe sepsis in India. Crit Care Med. 2007; 11:65
9. Calandra T, Cohen J. International Sepsis Forum Definition of Infection in the ICU

Consensus Conference. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005; 33:1538–48
10. Gendrel D, Raymond J, Assicot M, Moulin F, Iniguez JL, Lebon P, et al. Measurement of procalcitonin levels in children with bacterial or viral meningitis. Clin Infect Dis. 1997; 24:1240–2
11. Manegold C, Schmiedel S, Chiwakata CB, Dietrich M. Procalcitonin serum levels in tertian malaria. Malar J. 2003; 2:34
12. Chiwakata CB, Manegold C, Bönicke L, Waase I, Jülch C, Dietrich M. Procalcitonin as a Parameter of Disease Severity and Risk of Mortality in Patients with Plasmodium falciparum Malaria. J Infect Dis. 2001; 183:1161–4
13. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J RespirCrit Care Med. 2001; 164:396–402
14. Meisner M. Pathobiochemistry and clinical use of procalcitonin. ClinChimActa. 2002; 323:17–29
15. Müller B, Becker KL, Schächinger H, Rickenbacher PR, Huber PR, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med. 2000; 28:977–83
16. Chan YL, Tseng CP, Tsay PK, Chang SS, Chiu TF, Chen JC. Procalcitonin as a marker of bacterial infection in the emergency department: an observational study. Crit Care Med. 2004; 8:12–20
17. Whang KT, Steinwald PM, White JC, Nylen ES, Snider RH, Simon GL, et al. Serum calcitonin precursors in sepsis and systemic inflammation. J ClinEndocrinolMetab. 1998; 83:3296–301
18. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. Clin Infect Dis. 2004; 39:206–17
19. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. Intensive Care Med. 2000; 26:148–52
20. Sinha M, Desai S, Mantri S, Kulkarni A. Procalcitonin as an adjunctive biomarker in sepsis. Indian J Anaesth. 2011;55(3):266–270. doi:10.4103/0019-5049.82676

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