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Comparative Evaluation of PCT, CRP and IL-6 in Cases of Suspected Sepsis

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Abstract: ***Background: The diagnosis of sepsis is difficult, as clinical signs often overlap with other non-infectious causes of systemic inflammation. The study aims to compare the diagnostic efficacy of PCT, IL-6 and CRP levels in cases of sepsis in a tertiary care hospital. Materials and methods: A total of 55 patients were included in the study, who fulfilled the ACCPs Criterion for diagnosis of sepsis. Patient's serum samples were investigated to determine diagnostic efficacy of serum PCT, IL-6 and CRP. Results: Out of the 55 patients enrolled, PCT levels were high in 46 patients.89 % had raised CRP and 20 % had raised IL-6. Conclusions: The study concludes that PCT is a good diagnostic tool for early detection and management of sepsis which can be complimented by other parameters like CRP and IL-6.***

Keywords: Sepsis, Biomarkers, Procalcitonin, C-Reactive Protein, Interleukin- 6

1. Introduction

Sepsis is defined as "a life-threatening organ dysfunction caused by a dysregulated host-response to infection." Sepsis is a highly heterogeneous syndrome that is a net result of host and pathogen interactions triggering networks of biochemical mediators and inflammatory cascades. [1] Sepsis describes the body's systemic immunological response to an inflammatory process that can lead to end-stage organ dysfunction and death. There is evidence to show that the manifestations of sepsis can no longer be attributed only to the infectious agent and the immune response it endangers, but also to significant alterations in coagulation, immunosuppression, and organ dysfunction. [2] The diagnosis of sepsis is difficult, as clinical signs of sepsis often overlap with other non-infectious causes of systemic inflammation. [3] Patients frequently present to Emergency Department (ED), where distinguishing sepsis from non-infectious systemic inflammatory response syndrome (SIRS) is paramount for provision of timely, effective therapy. Current mainstay of sepsis therapy is early recognition and prompt antibiotic administration. However, the results of microbiological tests are usually significantly delayed and negative cultures do not exclude the presence of infection. [4] In addition, manifestations of sepsis such as fever, leukocytosis and tachycardia are neither specific nor sensitive for infection, nor for monitoring the response to therapy. [5]

Much effort has been directed towards the identification of biomarkers to aid in the clinical diagnosis and management of sepsis. Ideally, a sepsis biomarker should accomplish the following: decrease the time of diagnosis; differentiate between infectious and non-infectious cause of SIRS; reflect the effectiveness of antimicrobial treatment and other measures of source control; thereby lowering mortality and improving outcomes. [1] Multiple sepsis biomarkers have been investigated that meet one or more of these criteria, however, a gold standard biomarker has not yet been identified. Thus the approach is to shift focus to determine the diagnostic relevance of multiple biomarkers when used in concert [6]. Recently, there has been growing interest in Procalcitonin (PCT) as a biomarker that can guide the therapeutic decision making in the management of sepsis.

In the present study, we focus to determine and compare the diagnostic efficacy of PCT, IL-6 and CRP levels in patients of suspected sepsis and correlate them with clinically significant outcomes like infection likelihood, severity of sepsis, differentiating infectious and non-infectious SIRS in a tertiary care hospital like ours.

2. Materials and Methods

Aim of the Study

To study and compare PCT, CRP and IL-6 levels in patients admitted with the diagnosis of sepsis to the tertiary care facility.

Study Design

This was a prospective, observational and non-interventional study conducted in the Department of Microbiology, Government Medical College, Amritsar.

Study settings

The institutional ethical committee approval was taken. The informed and written consent was taken from patients before enrolling for the study. Over a 10 month period, a total of 55 patients, of either sex, admitted in GNDH were included in the study, who fulfilled the American College of Chest

Physician's Criterion (ACCP) for the diagnosis of sepsis (> 2 of the following) (a) Temperature > 38°C/< 36 °C (b) Heart rate> 100 bpm (c) Respiratory rate > 20 breaths/min or $paCO_2$<32 mm Hg (d) WBC count > 12, 000 cells/mm^3 or less than 4000 cells/mm^3 or > 10 % band forms. The relevant information of the patient along with case history, clinical details, risk factors, co-morbidities, was recorded.

Measurement of C-Reactive Protein, Procalcitonin and Interleukin-6

From the 55 patients, 5-10 ml blood was sampled under all aseptic precautions, for PCT, CRP and IL-6. Blood sample was clotted, centrifuged; serum separated and further stored at 2-8˚-20˚C until the day of assay.

- Testing for C-Reactive Protein was done by Quantitative turbidimetric Immunoassay.
- Testing for Procalcitonin and Interleukin-6 was done by Sandwich chemiluminescent immunoassay.

Statistical Analysis
The collected data was analyzed for mean, percentage and standard deviation. All the data was entered in MS EXCEL spreadsheet and analysis was done by using the Statistical Package for the Social Sciences-21 (SPSS)

3. Results

To analyze the value of PCT obtained, Patients were divided into four groups based on the severity of sepsis,

1) PCT> 10 ng/ml: Severe bacterial sepsis or septic shock
2) PCT 2-10 ng/ml: Severe systemic inflammatory response, most likely due to sepsis
3) PCT 0.5-1.9 ng/ml: SIRS; A systemic infection cannot be excluded
4) PCT < 0.5 ng/ml: Local bacterial infection possible; sepsis unlikely

Out of the 55 patients enrolled, 33 (60 %) were male and 22 (40 %) were female. Prolcalcitonin was raised in 34 patients. The minimum value of Procalcitonin which was obtained was 0.05 ng/dl and maximum was 51.55 ng/dl, Mean being 6.773 ng/dl; 9 patients had PCT <0.5 ng/dl with a median value of 0.066ng/dl; 13 patients had PCT between 0.5 and 1.9 ng/d, with a median value of 1.1ng/dl; 15 patients had PCT between 2-10 ng/dl, with a median value of 2.41 ng/dl; and 18 patients had PCT> 10 ng/dl with a median value of 11.746 ng/dl [Table 1]

Table 1: Procalcitonin levels distribution

PCT (ng/ml)	>10	02-10	0.5-1.9	<0.5
Sample size	18	15	13	9
Mean	17.33	3.698	1.146	0.094
Min value	10.55	2.3	0.63	0.001
Max value	51.55	7.74	1.615	0.9
Median	11.746	2.41	1.1	0.066

Distribution of IL-6 and CRP as per PCT levels: To study the correlation of PCT with IL-6 and CRP, IL-6 and CRP values were distributed in the above mentioned four PCT groups. The minimum value of IL-6 was obtained to be 0.5 pg/ml and maximum value was 382.6 pg/ml, with a mean value of 38.795 pg/ml. The mean IL-6 in 18 patients with severe sepsis was 66.16 pg/ml and in 15 patients with sepsis was 42.74 pg/ml. Out of the total 55 patients, 49 patients had CRP raised> 10 pg/ml.

The minimum value of CRP was obtained to be 2.8 mg/dl and the maximum q value was 141.3 mg/dl with a mean value of 41.23 mg/dl. The mean CRP in 18 patients with severe sepsis was 58.97 mg/dl and in 15 patients with sepsis was 34.52 mg/dl [Table 2]. Out of the total 55 patients, 11 patients had IL-6 raised> 43.5 mg/dl.

Table 2: Correlation of PCT value with CRP and IL – 6

PCT (ng/ml)	>10	02-10	0.5-1.9	<0.5
Sample size	18	15	13	9
Mean IL-6 (pg/ml)	66.16	42.74	16.04	10.56
Mean CRP (mg/dl)	58.97	34.52	30.02	23.76

4. Discussion

Sepsis is a complex, heterogeneous disorder that is frequently misdiagnosed with significant clinical consequences. The ability to diagnose or exclude suspected sepsis is vitally important to patient outcomes [1]. Several biomarkers have been investigated as a tool for early diagnosis of sepsis including Procalcitonin, C-Reactive Protein and IL-6.

PCT is an amino-acid polypeptide precursor for the hormone calcitonin. It was first identified in 1973 and first linked to infectious diseases in 1983. PCT offers favorable kinetics for a biomarker [7]. In our study, 33 out of 55 patients could be diagnosed as sepsis on the basis of PCT values. The range of PCT in patients with sepsis was 2.3-7.74 ng/dl and in septic shock was 11.746 ng/dl. The range of PCT obtained for SIRS was 0.63-1.615 ng/dl. These ranges are helpful in making a diagnosis of sepsis, if the PCT of the patient falls between the ranges.

In a study by Sharma *et al*, median PCT value was1.63 ng/ml for SIRS; 6.99 ng/ml for sepsis and 20.77 ng/ml for septic shock [6]. In a study by Harbarth *et al*, median PCT levels were 0.6 ng/ml for SIRS; 3.5ng/ml for sepsis; 6.2 ng/ml for severe sepsis and 21.3 ng/ml for septic shock [8]. The present study results thus confirms and extend earlier findings demonstrating that PCT is among the most promising biomarkers in critically ill patients, capable of complementing clinical signs and routine laboratory parameters suggestive of severe infection

IL-6 is a potent inflammatory marker and its plasma concentration has been used as a prognostic marker in critically ill patients. [8] IL-6 levels in patients with severe sepsis and septic shock were found to be significantly high. The mean value of IL-6 in sepsis was 42.74 pg/ml and in septic shock were 66.16 pg/ml, supporting the high PCT values in these two groups and thus supporting the diagnosis of sepsis and septic shock. However Il-6 levels were not significantly increased in patients with local bacterial infection and in patients with SIRS. Thus, no significant role of IL-6 was seen in diagnosis of SIRS.

CRP is a protein produced in response to infection and or/inflammation and is widely used to diagnose and manage patients with suspected sepsis [5]. The value of CRP was also significantly high in patients with sepsis and septic shock. Out of 55 patients, 49 had raised levels of CRP above 10 mg/dl. The minimum value of CRP was obtained to be 2.8 mg/dl and the maximum value was 141.3 mg/dl. The mean value of CRP in 15 patients with sepsis was 34.52 mg/dl and in 18 patients with septic shock was 58.97mg/dl. The value of CRP in 13 patients with SIRS was 30.02 mg/dl. Thus high level of CRP supported raised PCT levels and helped in the diagnosis of SIRS, sepsis and septic shock.

A meta-analysis by Wacker C et al evaluated 30 studies with 3244 patients yielded a sensitivity of 77 % and specificity of 79% indicating PCT as a useful diagnostic marker of early sepsis^. However, the most discriminatory CRP level has not yet been found and it may be different in diverse infections in patients with suspected sepsis. A study by Rau BM et al found PCT to be useful and better than CRP in predicting infections and multiorgan dysfunction syndrome in patients with suspected sepsis. Thus CRP response is considered as non-specific and should not be used as a single diagnostic tool. On the other hand, various studies have observed that IL-6 has limited diagnostic accuracy in critically-ill patients as it is raised nonspecifically due to the accompanying inflammation, independent of the infection, Whereas PCT rise is in response to an infection rather than inflammation. The present study supports the majority of the research conducted in regard to utility of PCT in sepsis.

5. Conclusion

The present study has helped us to diagnose cases of sepsis on the basis of biomarkers (PCT, CRP and IL-6). Among the biomarkers tested; it was observed that the severity of sepsis was correlated with the proportionate increased level of PCT. Thus, PCT is a good diagnostic tool for early detection, management of sepsis which can be complimented by other parameters like CRP and IL-6.

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Conflicts of interest
There are no conflicts of interest.

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