Original Research Article

Role of Procalcitonin and C-reactive protein in differentiating culture negative bacterial sepsis and systemic inflammatory response

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International Archives of Integrated Medicine, Vol. 4, Issue 3, March, 2017.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 14-02-2017 **Accepted on:** 18-02-2017
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: Siraj Ahmed Khan, Iyyapu Krishna Mohan, Bhavya Sirivelu, Rachel Jacob. Role of Procalcitonin and C-reactive protein in differentiating culture negative bacterial sepsis and systemic inflammatory response. IAIM, 2017; 4(3): 24-29.

Abstract

Background: It is very important to distinguish between non-infectious systemic inflammatory response (SIRS) and culture negative sepsis as the management of the two conditions is different this often creates diagnostic challenge in day to day practice. The aim of present study is to investigate the diagnostic accuracy of serum PCT and CRP to differentiate between culture negative bacterial sepsis and non-infective SIRS. We have also studied their diagnostic efficacy in culture-positive sepsis.

Materials and methods: 178 cases who were admitted in acute medical care unit in tertiary care centre, were included in the study. The cases were divided into three groups. Group I (culture positive sepsis) patients with positive microbial culture and 2 or more signs of sepsis. Group II (culture negative sepsis) includes patients with 2 or more sign of SIRs and clinical suspicion of infection with negative culture result. Group III (non-infective SIRs) includes patient with 2 or more sign of SIRS without evidence of any infection. Samples were collected for blood culture, differential count, PCT and CRP along with other routine investigation. The diagnostic performance of PCT and CRP was demonstrated with ROC curve analysis.

Results: The median Procalcitonin was approximately 9 fold higher in culture negative group compared to non-infective SIRS and it was statistically significant (P<0.01) whereas CRP showed

only 2-3 fold increase between these groups. ROC curve analysis for PCT and CRP between culture negative and SIRS groups for prediction of systemic infection were performed. The area under the curve for PCT and CRP were 0.986 and 0.785 respectively.

Conclusion: Biomarkers such as PCT and CRP are strongly associated with infection likelihood and sepsis and they can serve as useful adjuncts to routine clinical information. These markers were also able to distinguish between patients with non-infective SIRS and sepsis.

Key words

Procalcitonin, CRP, Non-infective SIRS.

Introduction

Patients in intensive care unit often present with similar complaints of high fever, abnormal heart and respiratory rate, the traditional marker of infection like fever, total leucocyte count may not be able to differentiate between infection, sepsis and non-infective systemic inflammatory response. Although microbiological culture is considered as gold standard for diagnosis of sepsis, a positive culture may be difficult to get in all cases and delay in culture reporting may cause loss of considerable precious time for treatment in cases of sepsis. The prevalence of infection in the intensive care unit study is reported as 30% for culture negative infection [1], these patients pose a challenge in decision making and subsequent treatment. According to surviving sepsis campaign recommendation, antibiotics should be administered within 1hour of septic shock [2] every hour of delay in antibiotic administration causes an increased mortality of 7.6% in septic shock [3]. Therefore early empirical treatment with antibiotic is lifesaving in such cases however these cases have to be differentiated from non-infective systemic inflammatory response syndrome (SIRS) commonly seen in patients with trauma, burns, pancreatitis and auto immune diseases such as Rheumatoid arthritis, SLE , etc. [4,5]. Therefore a specific biomarker with high sensitivity and specificity, which can diagnose and differentiate these two conditions, is of paramount importance for timely and appropriate treatment.

Inflammatory mediators have been identified in serum which is altered in sepsis and other conditions. Among these, procalcitonin (PCT) and C-reactive protein (CRP) have been studied widely, and shown to have a role in evaluation of severity of infection and sepsis [6-10]. Various studies have also been published showing significant relationship of PCT not only to infection and systemic inflammation, but also to organ dysfunction [4, 11].

Not many studies are available to show the role of PCT and CRP in differentiating culture negative bacterial sepsis and non-infective systemic inflammatory response. The aim of present study is to investigate the diagnostic accuracy of serum PCT and CRP to differentiate culture negative bacterial sepsis from non-infective SIRS. We have also studied their diagnostic efficacy in culture-positive sepsis.

Materials and methods

178 of cases who were admitted in Acute medical care unit in tertiary care centre in Hyderabad were included in the study. Inclusion criteria was age >18years, patients diagnosed with non-infectious SIRS, sepsis, severe sepsis or septic shock as per the established sepsis guidelines were enrolled in the study [12]. Patients who had received prior antibiotics, transferred from other ICUs, immunocompromised and with malignancy were excluded from the study.

Patients' demographics, principal diagnosis and all clinical parameters were recorded at the time of enrolment. Initial severity of illness was determined using the Acute Physiology and Chronic Health evaluation score (APACHE II).

Samples were collected for blood culture, differential count, PCT and CRP along with other routine investigations.

Two set of Sample for blood culture was collected in both aerobic and anaerobic BacT/Alert bottles and performed by BacT/Alert 3D system (France Biomeriex). PCT was done by sandwich immunoassay method on Cobas e411 (Roche diagnostic Germany) and CRP was done by Latex agglutination method.

Patients were divided into non-infective SIRS and suspected sepsis at the time of admission to the hospital based on clinical presentation by clinician. Culture negative and culture positive depending on microbial culture reports once results are available.

Group I (culture positive sepsis) patients with positive microbial culture and 2 or more signs of sepsis. Group II (culture negative sepsis) includes patients with 2 or more sign of SIRs and clinical suspicion of infection with negative culture result. Clinical infection was suspected depending on focus of infection and symptoms. Urinary tract infection was suspected in cases with sign and symptoms of urinary tract infection with presence of pus cells in urine. Pneumonia was suspected with history of cough, fever and lobar infiltration on X-ray. Similarly cellulitis was diagnosed by skin lesions.

Group III (non -infective SIRS) includes patient with 2 or more sign of SIRS without evidence of any infection.

Statistical analysis

Statistical analysis was performed using SPSS 17 software (SPSS, Chicago, IL). Continuous variables are presented as mean (range) or median (interquartile range) as appropriate. Categorical variable are presented as absolute number and percentage. Student 't' test was used to compare between the groups. Multiple group comparison was done with one way Annova.

The diagnostic performance of PCT and CRP was demonstrated with ROC curve analysis. The youden index was used to determine the optimal cut off value. P value <0.05 was considered as significant.

Results

A total of 178 patients with sepsis admitted in Emergency department were recruited in the study. These cases were divided into three groups group I culture positive cases (n=38), group II culture negative sepsis (n=64), and group III non infective SIRS (n=76). No statistically significant difference in sex and age was observed in between different groups. The number of female participant is more in group I and Group III and equal in Group II. Overall the number of female participant is more.

Procalcitonin and CRP levels were measured and analysed in all enrolled patients on the day of admission. The mean Procalcitonin was approximately 9 fold higher in culture negative group compared to non-infective SIRS and it was statistically significant (P<0.01) whereas CRP showed only 2-3 fold increase between the groups (**Table - 1**). However, levels of PCT and CRP were highest in culture positive groups. The WBC count though slightly high in culture negative group compared to non-infective SIRS was not statistically significant.

A significant difference was found between the mean levels of PCT, CRP and WBC count when three groups were compared (P<0.001).

ROC curve analysis for PCT and CRP between culture negative and SIRS groups for prediction of systemic infection were performed. The area under the curve for PCT and CRP were 0.986 and 0.785 respectively (**Figure - 1**). The optimal cut off for PCT was 0.5 ng/ml and 6 mg/l respectively.

Discussion

Sepsis is complex, heterogeneous disorder that is frequently misdiagnosed, with significant clinical

consequences [13-15]. The ability to diagnose or exclude suspected sepsis is vitally important to patient outcomes.

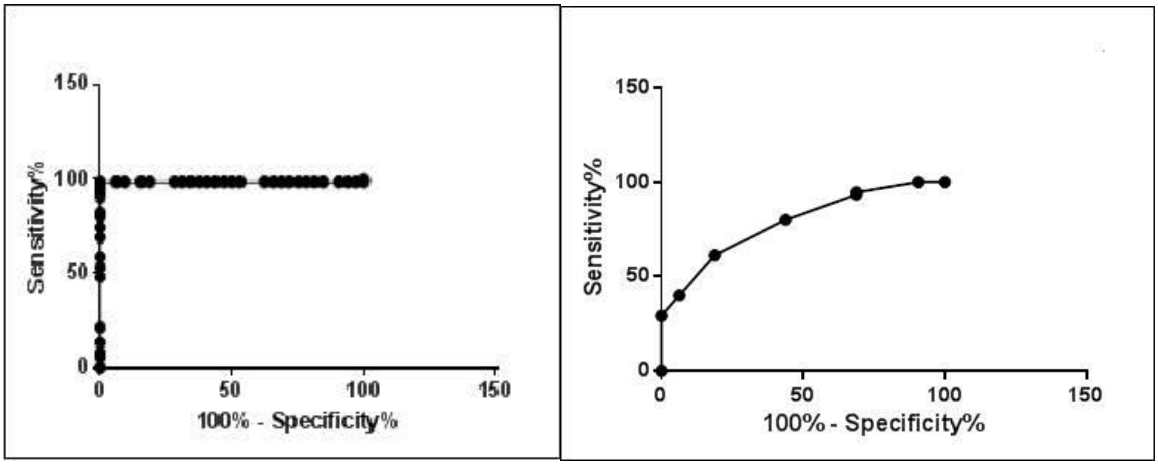
Blood culture testing has some disadvantage in diagnosis of sepsis as it is time consuming and many times it is not possible to isolate the organism. The efficiency of PCT and CRP in early diagnosis of sepsis has been studied earlier [16, 17].

Table - 1: Demographic and median value of variables in three study groups.

Variables	Group I	Group II	Group III	P value
Number of Patients	38	64	76	-
Sex male	16	32	30	-
Age (years)	38.13±17.2	52±10.17	46±14.51	NS
PCT (ng/ml)	41.98±31.34	9.23±7	1.1±0.13	<0.001
CRP (mg/l)	98.53±45.94	58.88±52.8	20.45±24.5	<0.001
WBC count (/mm^3)	12.9±4.9	10.8±3.5	8.8±8.1	0.004

All values expressed as mean±SD.

Figure - 1: Receiver operating characteristic curve for PCT and CRP between culture negative sepsis and non-infective SIRS.



But diagnosis of culture negative patient is difficult as it entirely depend clinically. The present study evaluates the ability of PCT and CRP in differentiating culture negative sepsis from non-infectious SIRS. PCT is synthesised by the C cell of thyroid gland and levels are detectable in plasma 2 to 3 hours after endotoxin injection in healthy volunteers. The half-life of PCT in serum is 25 to 30 hours [18].

CRP is an acute phase protein present in normal serum originally defined by its ability to precipitate pneumococcus C polysaccharide. Characteristically, CRP appears in the serum of individuals in response to various inflammatory conditions and tissue necrosis and disappears as the causative condition subsides.

We observed a high difference in PCT between culture positive and culture negative patients with AUC of 0.958 whereas CRP and WBC counts are significantly higher in patient with culture positive, they are not as discriminating as PCT, a finding consistent with other studies [19-21].

This study has shown a graded differentiation of PCT and CRP between 3 groups highest in

culture positive patients and lowest in non-infective SIRS. ROC curve analysis between culture negative and non-infective SIRS have shown a superior AUC for PCT then CRP. Thus, indicating the superiority of PCT over CRP in differentiating the culture negative sepsis from non-infective SIRS. These results are consistent with other studies [22].

Early diagnosis is key to effective treatment and timely intervention in sepsis patients. The quantitative estimation of PCT can be performed in half an hour and superior sensitivity of PCT as compared to CRP makes it an ideal marker for early diagnosis of sepsis both in culture negative and culture positive patients and to rule out non infective SIRS.

Our study has established the possible role of PCT and CRP to simplify the challenges of identification of culture negative sepsis patients in emergency department.

Limitation

The main limitation of our study was small sample size. A larger group and multicentre study was needed to extrapolate our finding.

Conclusion

Biomarkers such as PCT and CRP are strongly associated with infection likelihood and sepsis and they can serve as useful adjuncts to routine clinical information. These markers were also able to distinguish between non infective SIRS and sepsis.

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