



ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2019; 5(3): 172-176
www.allresearchjournal.com
Received: 11-01-2019
Accepted: 15-02-2019

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Procalcitonin as an early marker of invasive bacterial infection in febrile children aged 1 month to 5 years of age

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Abstract

Objectives: To evaluate the role of serum procalcitonin as a marker of invasive bacterial infection in febrile children between 1 month to 5 years of age. **METHOD:** Febrile Children aged between 1 month to 5 years with temperature at admission of $\geq 38^{\circ}\text{C}$ (100.4°F) and with no prior antibiotic use during the current febrile illness were studied prospectively.

Results: At a cutoff value of 2 ng/ml for serum PCT levels the sensitivity of 90%, specificity 76%, positive predictability value 78%, negative predictability value of 88%, area under curve (AUC) of 0.935 with standard error of 0.0221 and 95% confidence interval of 0.892 to 0.979 was obtained. The optimum sensitivity and specificity was 86% and 84% respectively at PCT level of ≥ 2.27 ng/ml.

Conclusions: Considering this high sensitivity and significant area under curve (AUC) it could be concluded that Serum PCT levels could serve a reliable early biomarker of invasive bacterial infection.

Keywords: Early biomarker, febrile children, invasive bacterial infection, pneumonias, procalcitonin, sepsis

Introduction

Fever is a state of elevated core body temperature above the normal daily variations due to increase in body's thermal set point. Normal body temperature varies through the day, but is generally less than 37.5°C centrally [1]. Fever is defined as presence of an axillary temperature $\geq 38^{\circ}\text{C}$ (100.4°F) taken for 3 minutes [2]. Fever can be due to a number of causes that include infections, connective tissue disorders, hypersensitivity diseases, neoplasm, granulomatous diseases, autoimmune diseases, etc., however, infections remain the leading cause of fever among children. Infections can be viral, bacterial, fungal, and parasitic in origin. Among bacterial infections, there can be localized, noninvasive or invasive infections. It is not always possible to differentiate between invasive and noninvasive bacterial infections with information gleaned from the medical history and physical examination [2]. Invasive bacterial diseases like Bacterial meningitis, Sepsis, Bone and joint infection (osteomyelitis), Acute pyelonephritis and Lobar pneumonia are a major cause of childhood morbidity and mortality. It has been estimated that 30% to 50% of children born in a rural setting are likely to die before the age of five years without timely and adequate medical intervention [3]. The majority of these deaths are not investigated as most health facilities lack the resources for conducting microbiologic studies [4]; furthermore, associated factors include delayed presentation to the hospital, poor health systems (low vaccine coverage) and infrastructure, and poorly motivated health staff [5]. Routine Diagnosis of invasive bacterial infection requires panel of investigations like Total leukocyte count, Differential leukocyte count, Urine examination and culture, CSF examination and culture, Blood culture, X-rays, and serum biomarkers like CRP Procalcitonin, various interleukins etc. In this study our emphasis is on Procalcitonin as a biomarker of IBI.

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis [6]. In contrast to the short half-life of calcitonin (10 minutes), procalcitonin has a long half-life of (25-30 hours) [7].

PCT is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine. PCT belongs to a different class of molecules, called "hormokines" The production of hormokines is mediated by as yet unknown factors and may be induced either directly via microbial toxins or indirectly via a humoral or cell mediated host response [8, 9].

The primary pathophysiological trigger for elevated level of PCT is infection [10]. Serum PCT levels are elevated in patients with bacterial infections, but are below the detection limit in healthy individuals and in patients with viral infections [11].

CRP determination results in an overprescription of antibiotics [12, 13]. Procalcitonin (PCT), the prohormone of calcitonin, was described as a new and innovative parameter of infection in 1993 [14]. Serum levels are very low in healthy individuals (<0.5 ng/ml) and in severe infections can reach up to 1000 ng/ml without changes in serum calcitonin levels [15].

Material and Methods

Study Design

We performed a prospective observational study in the department of pediatrics Sher-I-Kashmir Institute of Medical Sciences, Srinagar. This is an urban academic medical center in Srinagar, over a period of 3 years from January 1, 2016, through December 31, 2018. This study was approved by the institutional ethical committee. Informed written consent from parents of the infants was obtained.

Participants, Case definitions: Febrile Children aged between 1 months to 5 years with temperature at admission of $\geq 38^{\circ}\text{C}$ (100.4°F) and with no prior antibiotic use during the current febrile illness were included in the study. We defined case as febrile child with any of the following: bacterial growth in blood culture and/or CSF culture done with auto analyzer excepting CONS (in case of CONS positive blood culture, repeat blood culture was taken and repeat positive blood culture for CONS in a symptomatic patient was taken as positive), positive urine cultures taken from suprapubic tap/clean catch (in case of clean catch colony forming units $> 10^5$ was considered as significant), definite radiological evidence of lobar pneumonia on chest X-ray and/or CT chest read by 2 independent radiologists, definite evidence of osteomyelitis by CT /MRI scans, pus culture or bone biopsy. We excluded febrile children with any of the following: history of prior vaccination within 3 days of febrile episode, history of chronic illness, known case of immunodeficiency, patient on corticosteroids, lack of parental consent.

Data Collection and Laboratory Tests Measurement: All studied patients were evaluated as per standard predesigned format, which include recording age (in months) and other demographic variables including sex and socioeconomic status, drug history and details of current illness. Complete physical examination including anthropometry was noted from all the studied patients. Following investigations were done in all patients: Complete blood count, Blood culture, Urine analysis, Chest X-ray, CSF analysis and culture, PCT. Other investigations were done on case to case basis as per clinical condition of the patient. The samples required for these tests were collected on hospital admission, and were

immediately sent to the central laboratory of the institution for analysis. Complete blood count was done using Beckman Coulter CBC analyser, Blood culture using BACTEC method, Urine analysis and culture was done by suprapubic tap. CSF analysis and culture were done in case of suspected meningitis. CSF samples examined for protein, glucose, total and differential WBC. After centrifugation, the deposits subjected to manual Gram stain examination and microbiological culture. PCT was measured by a fluorescence immunoassay using QDX Instacheck.

Statistical Analysis: Data collected was entered in Microsoft excel sheet. Statistical analysis was done by using Statistical Package for Social Sciences (SPSS version 20.0; IBM Corporation, Armonk, NY). Results were presented as median, interquartile range (IQR), and percentages (%). Normality of continuous data was checked by Shapiro-Wilk test. Non parametric data was analyzed by Mann-Whitney U test. Nominal data was analyzed by chi square/Fischer's exact test.

Univariate comparisons between IBI and non-IBI groups were done using Student t tests for the continuous variables and chi-square tests for the categorical variables. $P < .05$ was considered statistically significant. The discriminative power of serum procalcitonin levels was determined by means of receiver operating characteristic curves. Further, the optimal statistical cutoff value for serum procalcitonin was calculated using receiver operating characteristic curve analysis.

Results

A total of 763 patients presented to our emergency department, of these 726 patients were enrolled in our study. Out of total 726 studied patients, 50 patients fulfilled criteria for definite invasive bacterial infection based on our definition. For comparison purposes 50 age matched control cases were taken from non invasive group.

Among 50 IBI patients, 16 were having meningitis, 21 pneumonia, 5 osteomyelitis, 7 pyelonephritis and 30 with sepsis. Of these patients, 24 (48%) patients were having negative blood cultures but fulfilled other criteria of case definition of IBI where as 26 (52%) patients were blood culture positive cases. Also 17(34%) develop septic shock and 11 (22%) patients expired. table 1.

Table 1: PCT values in cases (IBI) subgroup

Variables	Mean \pm SD PCT value	Percentage
Meningitis	32.65 \pm 35.29	16(32%)
Pneumonia	20.70 \pm 29.08	21(42%)
Osteomyelitis	22.45 \pm 7.40	5(10%)
Pyelonephritis	8.93 \pm 3.28	7(14%)
Sepsis	30.64 \pm 33.55	30(60%)

The mean and SD of serum PCT values of study group were obtained and compared table no. 2

Table 2: PCT values of Study Population

	Cases (n=50)	Controls (n=50)	p value
Mean \pm SD	20.94 \pm 28.59	1.68 \pm 1.50	0.00

Predictive Factors and Discriminative Power of Studied serum biomarker

The sensitivity, specificity, PPV and NPV of PCT at cut off value of 2ng/ml was obtained. Out of a total of 50 cases 45

patients who were having IBI were showing positive results for PCT and only 5 patients with IBI were having negative results for PCT so a sensitivity of 90%. Similarly 38 out of 50 patients in control group were negative for PCT and 12

were positive for PCT so a specificity of 76%, table 3. PCT value of $\geq 2\text{ng/ml}$ was taken as positive and $\text{PCT} \leq 2\text{ng/ml}$ was taken as negative.

Table 3: Showing sensitivity, specificity, positive predictibility value and negative predictibility value of PCT

	Cases	Control	Total
PCT Positive	45 (90%) True positive	12 (24%) False positive	57 (57%)
PCT Negative	5(10%) False negative	38(76%) True negative	43 (43%)
Total	50(100%)	50(100%)	100(100%)

Sensitivity	Specificity	PPV	NPV
90%	76%	78%	88%

Area under the curve (95% CI) for serum procalcitonin as a biomarker for invasive bacterial infection was 0.935 with standard error of 0.022 and 95% CI 0.892 -0.979. Optimum

cutoff PCT level of 2.27ng/ml was obtained with sensitivity and specificity was 86% and 84% respectively as shown in fig no. 1.and table no. 4. ROC curve for serum CRP was also obtained which showed (AUC) and 95%CI of 0.831 and 0.743 to 0.899 respectively as shown in fig. no. 2 and table no. 5.

Table 4: Test Result Variable(s)

Area under the Curve				
Test Result Variable(s): PCT				
Area	Std. Error ^a	Asymptotic Sig. ^b	95% Confidence Interval	
			Lower Bound	Upper Bound
.935	.022	.000	.892	.979

Table 5: Table showing Area under the curve (95% CI) for serum CRP as a biomarker for invasive bacterial infection

Area under the ROC curve (AUC)	0.831
Standard Error ^a	0.0411
95% Confidence Interval ^b	0.743 to 0.899
z statistic	8.054
Significance level P (Area=0.5)	<0.0001

Table 5 showing Area under the curve (95% CI) for serum CRP as a biomarker for invasive bacterial infection was

0.831 with standard error of 0.0411 and 95% CI 0.743 - 0.899.

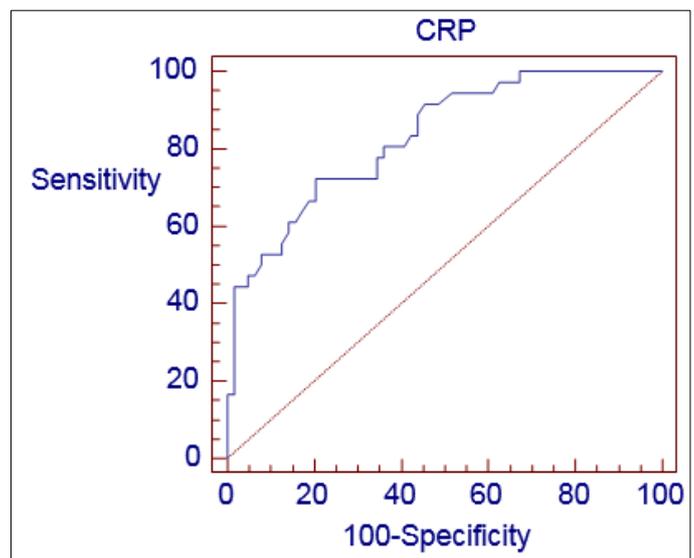
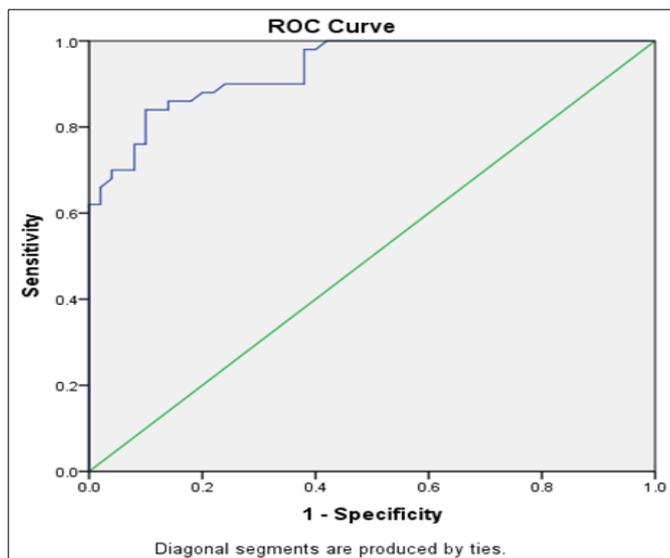


Fig 1-2: Respectively for PCT and CRP.

Discussion

In this study, we focused our analysis on possible role of serum PCT as early marker of invasive bacterial infections in febrile children, so that early intervention is done in invasive bacterial infections and also to avoid unnecessary hospital stay and overuse of antibiotics in noninvasive, local or viral febrile illness, which often are self-limiting. Furthermore, it is not always possible to differentiate

between invasive and noninvasive bacterial infections with information gleaned from the medical history and physical examination only [2]. Although blood culture is considered gold standard for diagnosing invasive bacterial infection, the initiation of antibiotic treatment often gets delayed as the results are available only after 24 to 48 hours. We report 50 cases of invasive bacterial infection in our study. Community acquired pneumonia (42%) was most

common IBI followed by meningitis (32%) and pyelonephritis (14%). A retrospective multicenter study in Korea on etiology of invasive bacterial infection in immunocompetent children between 2006-2010 revealed bacteremia without localizing signs as most common, accounting for 49% of IBI cases, followed by osteomyelitis 17%, meningitis 15% and pneumonia 12%. Likely reason for this difference in clinical syndrome presentation could be explained by the low level of pneumococcal vaccination coverage in this part of world. Which is further substantiated by the fact that respiratory infections were most common cause if IBI in the studies from countries where pneumococcal vaccination coverage is low. (Institute for health metrics and evaluation report, 2017).

The present study revealed significant mean elevation of PCT in invasive bacterial infection group, and serum PCT was able to differentiate invasive bacterial infection from noninvasive infection. In recent years there have been numerous studies which evaluated role of PCT as a marker of sepsis, bacteremia, meningitis, osteomyelitis, pyelonephritis, guiding antibiotic treatment and predicting results etc. Further there have been numerous studies comparing PCT with CRP as diagnostic marker of invasive bacterial infection. Sakr *et al* in their analysis reported serum PCT performs better than CRP in differentiating bacterial from non bacterial infection. Another study by Simon *et al* reported PCT has higher diagnostic accuracy as compared to CRP for bacterial infection.

In the present study the diagnostic accuracies of serum PCT and CRP were compared on area under ROC. AUC values 0.935 for PCT would be considered as diagnostically “excellent” test and 0.831 for CRP as diagnostically “good” test in differentiating invasive bacterial infection from non invasive infection. LOPEZ AF and coworkers reported AUC of 0.82 and 0.78 respectively for PCT and CRP in differentiating bacterial and viral illness. Similarly Herthetrill-M *et al* reported AUC of 0.96 and 0.83 for PCT and CRP respectively.

We intended to identify a ‘cutoff’ for serum PCT, that can be called significant for presence of invasive bacterial infection in children. The optimal cut-off values studied for serum PCT vary widely between different studies^[16]. In healthy people, plasma concentrations of PCT are typically below 0.05ngml⁻¹, but can rise to level of 1000ngml⁻¹ in conditions of sepsis or septic shock^[16, 17]. We observed, at a ‘cutoff’ value of 2ng/mL as positive for PCT as per the guidelines of manufacturer company, asensitivity, specificity, positive predictability value and negative predictability value were 90%, 76%, 78% and 88% respectively. The optimum sensitivity and specificity was 86% and 84% respectively at PCT level of ≥ 2.27 ng/ml. The similar results were reported by Hatherill M *et al* and LOPEZ AF *et al* in their studies though cutoff used there was 0.5ng/ml. Considering the high morbidity and mortality of invasive bacterial infection it would be extremely valuable to find a cost-effective, reliable, and readily available marker with high diagnostic efficiency to pick out invasive bacterial infection at their earliest. Our results present further indication that PCT is a best marker for this purpose especially at cut off value ≥ 2.27 ng/ml of serum PCT.

Giamarellou *et al* (2004) reported that PCT is a helpful marker for detection of bacteremia, severe sepsis, and local bacterial infection but PCT levels were not significantly

elevated in CNS bacterial infection in their study. The present study and the study done by Ilbrahim KSA *et al* demonstrate serum PCT levels were significantly higher in bacterial meningitis. However contrarily to our results de Bont *et al* demonstrated no significant increase in PCT levels in bacterial infection in febrile neutropenic patients. The possible reason for this ambiguity could be explained by the fact of neutropenic patients doesn’t mount normal immune and PCT response, which is a known acute phase reactant.

The novelty of our study is that, to our knowledge this is the first study from India to evaluate the performance of serum procalcitonin as an early marker of invasive bacterial infection in febrile children from one month to 5 years of age. However our study has limitations, first the data were from a single medical institute, so the findings may not be generalized. Second, our control group is non homogenous including both viral and bacterial infected febrile children so there is possibility of overestimation of actual results.

Conclusion

Our results indicate that the serum procalcitonin as biomarker has high sensitivity and specificity in detecting patients with IBI, and when compared with CRP it has better test characteristics. Procalcitonin levels at admission in a febrile child can guide initiation of early treatment in IBI and help avoid unnecessary over prescription of antibiotics, in non invasive bacterial, viral febrile illnesses. Being a rapid and bedside investigation, early evaluation and consequent management in invasive bacterial infections may significantly decrease the morbidity and mortality among children.

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