

Assessment of Serum Procalcitonin Level in Children with Community Acquired Pneumonia

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Abstract:

Community Acquired Pneumonia (CAP) is a leading cause of mortality in children. Procalcitonin (PCT) is produced by C cells of the thyroid. PCT is released from extra thyroidal tissues during infections. In CAP, serum PCT is significantly raised and measuring serum PCT may aid physicians in predicting severity and reducing total antibiotic use.

Objective: To observe diagnostic significance of Procalcitonin level in paediatric CAP and its association with severity and also association of PCT level with time taken for recovery.

Methods: This was a case control observational study conducted in tertiary care hospital. PCT was measured in 60 patients aged 2 to 59 months and compared with 60 controls. Procalcitonin assay was done by sandwich ELISA. ROC curve analysis was performed for diagnostic accuracy. PCT levels were compared between pneumonia and severe pneumonia. Prognostic significance was determined in relation to time taken for recovery.

Results: Mean age of CAP cases was 14.98(±14.50) months. 41 were males and 19 were females. The mean PCT was 2.37±1.24 ng/mL in CAP patients compared to 0.26±0.15 ng/mL in controls which was significant ($p < 0.0001$). The area under ROC for PCT was better than both ESR and CRP but not significantly higher than CRP. There was no significant difference of PCT level in pneumonia and severe pneumonia. Among 58 patients with raised PCT, 16 recovered in <10 days, 39 recovered in ≥10 days ($p = 0.0077$) which was statistically significant.

Conclusion: PCT level was found to be significant diagnostic and prognostic marker for CAP patients but could not assess severity.

Keywords: Community acquired pneumonia (CAP), Children, Procalcitonin (PCT).

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I. Introduction

Pneumonia is a leading cause of mortality in children. CAP is one of the most common respiratory disorders in children, which necessitates frequent hospitalization.¹ CAP can be defined clinically as the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital.² In developed countries this can be verified by the radiological finding of consolidation. In the developing world a more practical term acute lower respiratory tract infection is preferred, reflecting the difficulties in obtaining an X-ray.²

Procalcitonin (PCT) is a 116-amino-acid residue peptide with molecular weight of about 13 kDa.³ In 1993, PCT was described as a new and innovative parameter of infection.⁴ In the traditional endocrine view, PCT is produced mainly in neuroendocrine C cells of the thyroid. Its production is governed by the calcitonin I (CALC-I) gene on chromosome 11p15.2-p15.1. Plasma PCT was shown to be very low in healthy individuals (<0.5 ng/mL), while it elevates in severe bacterial infections and septic conditions, where it can reach up to 1,000 ng/mL.^{5,6,7}

As per our knowledge, no similar study has been done on a pediatric population in North-Eastern region of India & hence we are undertaking this study in our institution with the following aims and objectives.

II. Aims And Objectives

To observe the diagnostic significance of Procalcitonin level in pediatric community acquired pneumonia and its association with severity and also to observe the association of the Procalcitonin level with time taken for recovery.

III. Material And Methods

The study was a hospital based case control observational study conducted in Department of Pediatrics, Assam Medical College & Hospital, Dibrugarh, Assam, India for the period of one year from July 2016 to June 2017. 60 children aged 2-59 months with the diagnosis of CAP were enrolled in the study and 60 age and sex matched healthy children were taken as controls.

Study Design: Hospital based case control observational study.

Study Location: Department of Pediatrics, Assam Medical College & Hospital, Dibrugarh, Assam, India.

Study Duration: One year from July 2016 to June 2017.

Sample size: 60 cases and 60 controls

Subjects & selection method: 60 children aged 2-59 months with the diagnosis of CAP were enrolled in the study and 60 age and sex matched healthy children came to well baby clinic were taken as controls.

Inclusion criteria: Children of 2month - 59 months having pneumonia and severe pneumonia/very severe disease fulfilling the clinical criteria according to Revised WHO Classification were included in the study.¹⁰

Exclusion criteria: Patient who has been hospitalized and treated with antibiotics for > 48 hours, patients having congenital heart disease, patient with chronic heart, lung, neurological disease, tuberculosis, HIV and malignancy, parents not willing to participate.

Procedure methodology:

A venous blood sample was drawn from each child for total white blood cell count, differential count, C-reactive protein, ESR, Procalcitonin and blood culture. For Procalcitonin assay a serum separator tube was used and samples were allowed to clot for 2 hours at room temperature or overnight at 4°C before centrifugation for 20 minutes at approximately 1000 xg. The supernatant was collected & immediately stored at -80 °C. Procalcitonin values were assayed by a commercial ELISA kit (sensitivity 15 pg/ml).¹¹ The laboratory team performed this test and were blinded to the clinical data.

A chest X-ray was done in every child. If a pleural effusion was present, a pleural liquid sample was drawn and sent for analysis and culture. A predesigned proforma was filled up for each patient to record all the necessary information like demographic profile, clinical features, physical examination findings, laboratory findings and duration of hospital stay.

We have categorized the patients into pneumonia and severe pneumonia on the basis of clinical presentations at admission according to Revised WHO classification and treatment of childhood pneumonia at health facilities (2014).¹⁰

Statistical analysis:

Continuous variables were expressed as mean \pm standard deviation and compared with student t- test. The area under ROC curves (AUROC) of serum PCT, CRP and ESR for diagnosis of CAP were calculated. The diagnostic accuracy values of sensitivity, specificity and likelihood ratio were calculated. The optimal cutoff values were set for diagnosis of CAP. The level of significance was set at 0.05. Data were analyzed by Microsoft Excel 2010, MedCalc® Version14.8.1.

IV. Results

Mean age of CAP cases was 14.98 months (\pm 14.50months). 28 cases belonged to age group 2 months to <6 months (46.67%), 15 cases belonged to age group 6 months to <24 months (25%) and 17 cases belonged to age group 24- 59 months (28.33%). 41 (68.33%) patients were males and 19 (31.67 %) were females.

The mean PCT was 2.37 ± 1.24 ng/mL in CAP patients compared to 0.26 ± 0.15 ng/mL in healthy controls which was highly significant ($p<0.0001$). The mean CRP and ESR were also significantly higher in cases compared to controls($p<0.0001$). (Table:1)

The area under ROC (AUROC) for serum PCT was better than those of ESR which is statistically significant (AUC 0.981 vs. AUC 0.922 with $p=0.0358$) and also better than CRP but not statistically significant. The optimum diagnostic cut off point for serum PCT level in the study was 0.3 ng/mL, CRP was 0.66mg/dl and ESR was 25mmAEFH (Fig:1 and Table:2)

13 cases were blood culture positive and 6 cases had empyema thoracis. Out of 13 culture positive cases 12 cases (92.31%) has raised PCT (9 has PCT >2ng/ml, 2 has PCT>1ng/ml, 1has PCT>0.3ng/ml) and out of 6 empyema cases all 6 had (100%) has raised PCT level (>1ng/ml).

Out of 60 cases 58 cases had raised PCT. Among them 16 patients recovered in <10 days and 39 cases (67.2%) recovered in ≥ 10 days ($p=0.0077$).

Out of 60 cases 19 cases were pneumonia with mean \pm SD of PCT = (2.34 \pm 1.44)ng/mL and 41 cases were severe pneumonia with mean \pm SD of PCT= (2.39 \pm 1.15)ng/mL. PCT is not significantly raised in severe pneumonia compared to pneumonia cases ($p=0.8856$). (Fig:2)

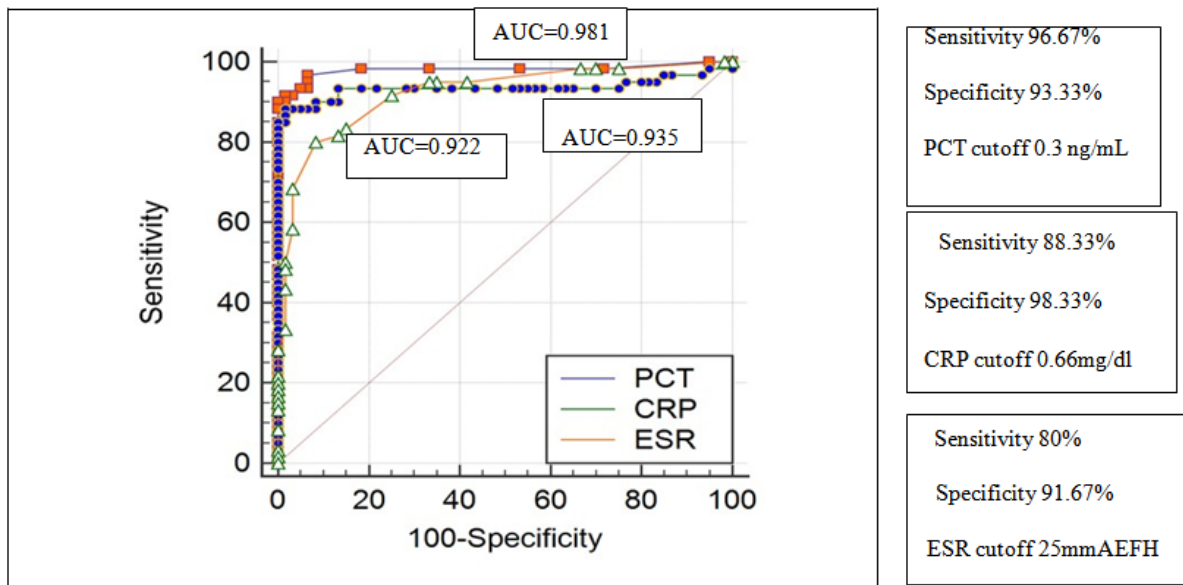
Table: 1 PCT and other inflammatory markers in cases and controls

		CASES (n = 60)	CONTROLS (n = 60)	<i>p value</i>
PCT (ng/mL)	Mean \pm S.D.	2.37 \pm 1.24	0.26 \pm 0.15	<0.0001
CRP (mg/dl)	Mean \pm S.D.	4.35 \pm 5.44	0.40 \pm 0.13	<0.0001
ESR (mmAEFH)	Mean \pm S.D.	47.52 \pm 26.43	13.22 \pm 9.65	<0.0001

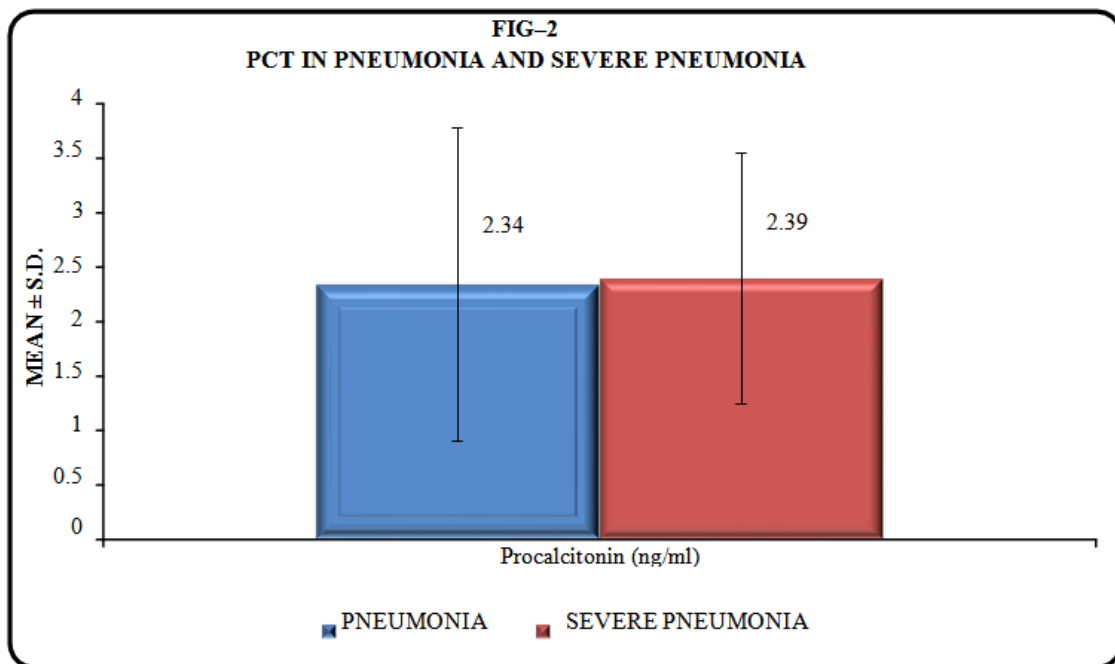
Table: 2 Cutoff values of all inflammatory markers after ROC analysis

	Cut off value	AUC	Youden Index J	Sensitivity (%)	Specificity (%)	<i>p value</i>	95%CI
ESR (mmAEFH)	>25	0.922	0.7167	80	91.67	<0.0001	0.858-0.963
CRP (mg/dl)	>0.66	0.935	0.8667	88.33	98.33	<0.0001	0.874-0.972
PCT (ng/ml)	>0.3	0.981	0.9000	96.67	93.33	<0.0001	0.937-0.997

Fig: 1 ROC Curve



The optimum diagnostic cut off point for serum PCT level in the study was 0.3 ng/ml (AUC =0.981; 95%CI,0.937-0.997), CRP was 0.66mg/dl (AUC = 0.935;95%CI,0.874-0.972), and ESR was 25mmAEFH (AUC = 0.922;95%CI,0.858-0.963) by the ROC curve analysis. (Using MedCalc® Version 14.8.1) Abbreviations: PCT- procalcitonin, CRP- C reactive protein, ESR- erythrocyte sedimentation rate, AUC- area under the curve, ROC curve- receiver operating characteristic curve.



V. Discussion

In the present study after taking 0.3ng/ml as a cut off value from ROC analysis 58 cases out of 60 (96.66%) showed PCT>0.3ng/ml compared to 3 controls (5%) which is highly significant(p<0.0001). So for our study population 0.3 ng/ml should be the cut off value to diagnose community acquired pneumonia.

The area under ROC (AUROC) for serum PCT was higher than those of CRP but not statistically significant (p = 0.1484) and significantly higher than ESR (p = 0.0358). The optimum diagnostic cut off point for serum PCT level in the study was 0.3 ng/ml (sensitivity=96.67%, specificity=93.33%), CRP

level was 0.66mg/dl (Sensitivity=88.33%, Specificity=98.33%), and of ESR was 25mmAEFH (Sensitivity=80%, specificity=91.67%) by the ROC curve analysis.

We can compare our study with the study by Jin Yong Lee et al,¹² where the area under the ROC (AUROC) for serum PCT was significantly higher than both CRP and ESR ($P<0.01$) whereas in our study AUROC for PCT was significantly higher than ESR but not CRP. The optimum diagnostic cutoff point for the serum PCT, CRP, ESR levels in the study by Jin Yong Lee et al¹² was 1ng/mL (sensitivity=90%, specificity=83%), 0.6 mg/dl (sensitivity=90%, specificity=88%), 30 mm/hr (sensitivity=80%, specificity=72%), by the ROC curve analysis.

We divided the CAP children into pneumonia and severe pneumonia or very severe disease according to Revised WHO Classification and Treatment of Pneumonia in Children at Health Facilities¹⁰. We have included CAP patients with bacteraemia (positive blood culture) and empyema in complicated pneumonia group.

In our study 19 (31.67%) patients were pneumonia and 41 (68.33%) cases were severe pneumonia/very severe disease. In this study PCT level is $>0.3\text{ng/mL}$ (cut off taken from ROC curve analysis for PCT) in 18 patients (94.74%) out of 19 pneumonia patients and 40 cases (97.5%) out of 41 severe pneumonia cases. For pneumonia the mean PCT level was $2.34 \pm 1.44 \text{ ng/mL}$ and for severe pneumonia mean PCT level was $2.39 \pm 1.15 \text{ ng/mL}$. No significant difference is seen in PCT level between pneumonia and severe pneumonia/ very severe disease ($p=0.8856$).

In another study by Luisa Agnello et al,¹³ results did not show an advantage in the use of PCT in comparison with CRP in order to evaluate disease severity in children with CAP. Distribution was shown by PCT quartiles of the main clinical and radiographic findings known to be associated with CAP severity in children but they did not find any significant association. This study correlates to the present study.

Don M. et al,¹⁴ in 2007 studied efficacy of serum procalcitonin in evaluating severity of community-acquired pneumonia in childhood on 100 children. PCT was higher in patients that were admitted than as outpatients (medians 17.81 vs. 0.72 ng/mL, respectively, $p<0.01$) and higher in alveolar than in interstitial pneumonia (medians 9.43 vs. 0.53 ng/mL, respectively, $p<0.01$). In conclusion, serum PCT values were found to be related to the severity of CAP in children even though they were not capable, at any level of serum concentration, to differentiate between bacterial and viral etiology.

In a very recent publication by Nicola Principi et al¹⁵ in 2017, it was mentioned that among traditional biomarkers, PCT appears to be the most effective both in selection of bacterial cases and in evaluation of severity in children with CAP. However, a precise cut-off level able to separate bacterial from viral cases and mild from severe cases has not been defined.

In the present study median duration of hospital stay was 12 days. Out of 60 cases 58 cases had $\text{PCT}>0.3 \text{ ng/mL}$. Among these 58 patients 16 (27.5%) recovered in < 10 days, 39 patients (67.2%) recovered in ≥ 10 days ($p=0.0077$) which was statistically significant. In this study 3 patients with CAP died. All these 3 patients had $\text{PCT value}>2\text{ng/dl}$. In another study by Lalita Fernandes¹⁶, in adult patients, demonstrated that PCT level risk class at admission is an excellent test to predict 30 day mortality in community acquired bacterial pneumonia. The median duration of hospital stay was 7.0 (6, 10) days.

In this study test for virus isolation was not done. Therefore, the use of serum PCT to differentiate bacteria from virus requires further confirmation. In order to determine the duration of high PCT level in serum, further study is required; serial measurements were not obtained in this study. The PCT levels were measured at the time of admission only. The onset of disease prior to admission across the patients. Therefore, the PCT level at the time of admission may not represent the peak PCT levels in the patients.

VI. Conclusion

We can conclude that PCT is a significant diagnostic as well as prognostic marker of CAP but cannot assess disease severity in this setting. Although several evidences supported a diagnostic and prognostic role of PCT in pneumonia, especially in adults, its contribution in pediatric Community Acquired Pneumonia has not fully elucidated. A multicenter study with longer duration and with larger number of patients is warranted to throw more light in this regard.

Contributors: RB: collected, compiled, analyzed the data, drafted the initial manuscript and designed the study. LB: conceptualized and designed the research plan, supervised and finalized the manuscript.

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