Original Research Article

Utility of Procalcitonin as a Prognostic Marker in Critically Ill Children with Suspected Bacterial Infection: A Prospective Observational Study

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Received: 28-11-2021 / Revised: 28-12-2021 / Accepted: 09-01-2022

Abstract

Introduction: Sepsis in pediatric population is the cause of substantial morbidity and mortality. The clinical manifestations range from subclinical infection to severe manifestations of focal or systemic disease. Various markers of sepsis are available to diagnose and interpret early an ongoing sepsis. **Aim:** To evaluate the utility of procalcitonin levels in predicting the severity and prognosis of critically ill children in our hospital setup. **Materials and Methods:** This was a prospective, observational study of 80 children who were admitted to PICU. Serum PCT samples within 12 hours of admission was sent for evaluation in pathology lab. PRISM-III, PIM-2 and MODS was calculated at the time of admission. The duration of stay in PICU and outcome in the form of discharge or death was recorded. **Results:** PCT levels were elevated in most critically ill children admitted to PICU with suspected bacterial infection. 81.2% had elevated PCT levels with mean value of baseline PCT 37.4 ng/mL. Children who developed complications during hospital stay had significantly high levels of PCT. The correlation between PCT and severity scores (PRISM III score or PIM2 score) was poor but significant (ρ-0.333, p=0.0025 and ρ-0.3437, p=0.0018). **Conclusions:** PCT levels were high in patients who were critically ill, who developed complications during hospital stay and died in hospital. PCT is a better diagnostic marker for predicting severe sepsis, septic shock, multi organ dysfunction and mortality.

Keywords: bacterial infection, procalcitonin, prognostic marker, sepsis, septic shock

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Introduction

Critical illness is a leading cause of morbidity and mortality in children and they often have sepsis and/or septic shock for which ICU admission is required. Sepsis often leads to organ dysfunction which complicates the management and affects the outcome of sepsis/septic shock[1].

Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the prompt need of appropriate interventions, if not already being instituted. Lack of early diagnosis and timely intervention for sepsis increases mortality, prolongs duration of hospital stay and increases healthcare costs.

There has been a lot of research in the development of putative biomarkers for critically ill children like CRP, Absolute Neutrophil count (ANC), Total Leukocyte Count (TLC), Bandemia and newer markers including Procalcitonin, IL-8, nGAL, Adrenomedullin and prosepsin[2,3,4].

Various scales have been developed to estimate the mortality risk in these sick children depending on clinical signs and routine investigations. Some of the useful ones are Pediatric Risk of Mortality (PRISM III), Pediatric Index of Mortality (PIM 2). Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality[5].

PCT is the pre-hormone of calcitonin, secreted by the C cells of thyroid in response to hypercalcemia. During pro-inflammatory states, endotoxins and inflammatory cytotoxins (i.e., TNF-α, IL-1, and IL-6) stimulate the production of PCT in the lungs, liver, intestine and peripheral mononuclear cells.

These cells cannot cleave PCT into calcitonin, elevating serum PCT, typically within 3–4 hours of endotoxins release and peaks at 24 hours, provided no second infectious hit occurs[6,7,8].

PCT differs from other proposed sepsis markers such as cytokines, CRP or lipopolysaccharide binding protein (LBP) primarily by the fact that it better reflects the severity of the systemic inflammatory response to infection[9] and it has been shown to have some potential to differentiate between the infectious and non infectious causes of systemic inflammation.

There is increasing evidence on PCT in critical illness in adult population. Evidence suggests that PCT has crucial role in successful treatment and positive outcomes, is an early diagnosis and differentiation from non-infectious causes, in order to rapidly start with antimicrobial therapy and fluid resuscitation[10]. However, pediatric data is lacking. There is heterogeneity in etiologies of pediatric ICU admissions in developed and developing countries. Data on PCT from developing countries on PCT in critically ill children is lacking.

We planned to prospectively evaluate the utility of procalcitonin levels in predicting the severity and prognosis of critically ill children in our hospital setup.

Methods

This prospective observational study was conducted at Pediatric Intensive Care Unit of a tertiary care hospital in New Delhi from May 2016 to April 2017. After obtaining Institutional Ethical Committee approval, we enrolled consecutive 80 critically ill children with suspected bacterial infection in the age group of 1 month to 12 years admitted to the PICU. Patients with trauma, surgical issues, burns and auto-immune disorders were excluded from the study.

Following informed written consent from the parents, children fulfilling inclusion criteria were enrolled in the study. Patients were managed as per standard pediatric ICU guidelines for management of

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the respective illness. Relevant investigations were performed wherever indicated.

Serum sample for PCT was obtained within 12 hours of PICU admission and analysed in the hospital laboratory using VIDAS® B.R.A.H.M.S PCT™. It has sensitivity of 96.9% and specificity of 67% for 0.5ng/ml cut off value of PCT. The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection (ELFA). A serum concentration of >0.5ng/ml, was considered as elevated.

PRISM-III, PIM-2 and SOFA score were calculated at the time of admission. Need for respiratory support, vasopressor support, renal replacement therapy and other advanced life care support was noted. The patient after being assessed by treating physician as fit/ stable were shifted to ward and the duration of stay in hours in PICU was recorded. Outcome in the form of discharge or death was also noted.

Baseline value of PCT and severity scores were compared in terms of better prediction of outcome. PCT and CRP were also compared for prediction of severity of illness.

Statistical analysis

The data was entered in Microsoft Excel sheet and analyzed by Statistical software (Version 12). Categorical variables were presented as proportion and continuous variables were presented as mean (±SD) or median (IQR). For comparision between two groups, t-test was used for normally distributed continuous variables, and Wilcoxon rank sum test was used for non-normally distributed continuous variables. Chi-square test or Fischer exact test were used for categorical variables. A difference between 3 or more groups was performed by using ANOVA or Kruskal-Wallis test. Spearman's correlation was used for correlation between PCT and PRISM-III, PIM-2 and MODS. ROC curve was drawn to assess the predictive value of PCT, CRP and TLC for severity of sepsis, organ dysfunction and mortality. P value < 0.05 was considered as significant.

Results

Eighty critically ill patients in the age group of 1 month to 12 years of age were enrolled in the study. The baseline characteristics were as shown below.

Table1. Baseline characteristics of enrolled patients

Baseline Characteristics	Observations (n = 80)
Age, months, mean (SD)	34.7 (±39.4)
Gender: Male, n (%)	47 (58.8)
Female, n (%)	33 (41.3)
Vitals on Admission:	
Tachycardia, n (%)	40 (50)
Tachypnea, n (%)	73 (91.3)
Temperature: Fever, n (%)	50 (62.5)
Hypothermia, n (%)	5 (6.3)
Shock, n (%)	17 (21)
PRISM III, median (IQR)	5.5 (3.5-17)
PIM 2, median (IQR)	2.4 (1.4-10.4)
Multi Organ dysfunction, n (%)	31 (38.8)
Duration of PICU Stay, hours, mean (SD)	106.7 (±115.9)
Duration of Hospitalization, hours, mean (SD)	177.7 (±147.7)
Need Of Mechanical Ventilation, n (%)	28 (35)
Need Of Any Respiratory Support, n (%)	70 (87.5)
Need of Vasopressors, n (%)	18 (22.5)
Need of Blood Products, n (%)	27 (33.8)
Presence of AKI, n (%)	10 (12.5)
Presence of Coagulopathy, n (%)	15 (18.8)
Mortality, n (%)	18 (22.5)
SIRS, n (%)	76 (95)
Sepsis, n (%)	70 (87.5)
Severe Sepsis, n (%)	32 (40)
Septic Shock, n (%)	17 (21.3)

Table 2: Baseline PCT levels in enrolled patients

PCT levels (ng/mL)	n (%)
≤ 0.5	15 (18.8)
>0.5 < 10	29 (36.2)
≥10 < 50	20 (25)
≥50 < 100	6 (7.5)
≥100	10 (12.5)

The correlation between PCT and severity scores (PRISM III score or PIM2 score) was poor but significant (ρ-0.333, p=0.0025 and ρ-0.3437, p=0.0018). PCT had modest correlation with multiorgan dysfunction score (ρ-0.5130, p<0.0001). There was no correlation between PCT and duration of PICU stay (ρ- 0.1491, p-0.1870).

Table 3: Correlation between PCT levels and severity of illness

	Rho value	P value
PCT and Prism III score	0.333	0.0025
PCT and PIM 2	0.3437	0.0018
PCT and Multi Organ dysfunction Score	0.5130	<0.0001
PCT and Duration of PICU stay	0.1491	0.1870

Comparison between PCT and CRP in relation to severity score

We classified the study children into three groups based on PRISM III values. Children with PRISM III ≤10 were labeled as mild severity, >10 ≤ 20 as moderate severity and >20 as severe illness

Table 4: Relation of PCT and CRP with PRISM III score

PRISM III Score	n (%)	PCT (ng/mL)	P value	CRP (mg/dL)	P value
0 ≤ 10	53(66.25)	16.9 (±38.1)	0.0050	11.4 (±10.1)	0.6825
>10 ≤ 20	14(17.5)	55.6 (±66.9)		13.1 (±8.3)	
>20	13(16.25)	101.5 (±91.4)		11.6 (±9.7)	

Table 5: Relation of PCT and CRP with Multi organ dysfunction score (MODS)

Multi-Organ Dysfunction score	n (%)	PCT (ng/mL)	P value	CRP (mg/dL)	P value
Yes	31 (38.8)	82.9 (±82.3)	**<0.0001**	14.2 (±10.5)	0.1163
No	49(61.3%)	8.6 (±11.3)		10.2 (±8.8)	

Secondary outcome

A. Complications during hospital stay

Children who required mechanical ventilation, vasopressors support, developed AKI, coagulopathy and needed blood products had significantly high levels of PCT.

Table 6: Complications during hospital stay and PCT and CRP values

Complications during hospital stay		PCT(ng/mL)	P value	CRP(mg/dL/)	P value
Need Of Mechanical Ventilation	Yes	77.4(±80.1)	0.0005	14.14(±10.5)	0.1394
	No	15.8(±37.6)		10.41(±8.9)	
Need Of Any Respiratory Support	Yes	41.0 (±66.6)	0.9710	11.6 (±9.7)	0.6467
	No	12.1 (±11.9)		12.6 (±9.9)	
Need Of Vasopressor support	Yes	116.6 (±85.2)	0.0001	14.4 (±11.1)	0.3189
	No	14.4 (±27.2)		10.9 (±9.1)	
Presence Of AKI	Yes	131.4 (±87.6)	0.0003	17.7 (±8.3)	0.0270
	No	24.9 (±45.7)		10.9 (±9.6)	
Need of blood products	Yes	79.2 (±82.9)	0.0001	15.4 (±9.9)	0.0084
	No	16.1 (±35.2)		9.8 (±8.9)	
Coagulopathy	Yes	114.1 (±85.0)	<0.0001	16.7 (±10.7)	0.0356
	No	19.7 (±40.4)		10.6 (±9.1)	
Mortality	Survivors	17.9 (±36.0)	0.0018	11.1 (±9.0)	0.5376
	Non- survivors	104.6 (±87.6)		13.7 (±11.6)	

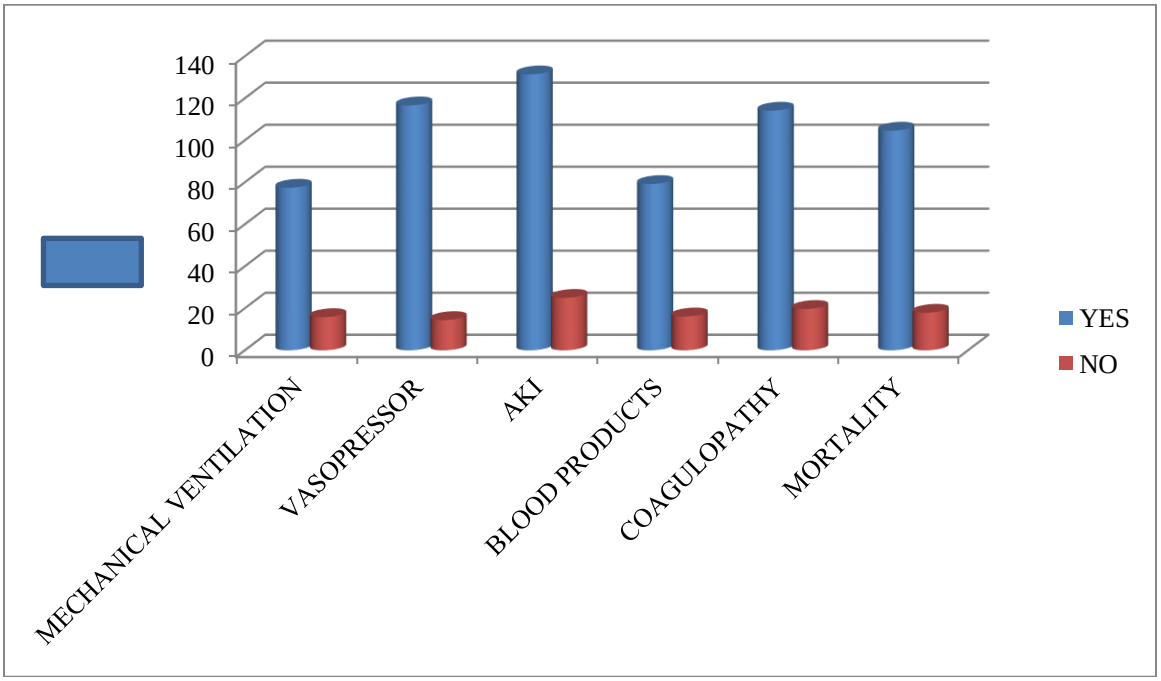

Figure 1: Relation of PCT levels with complications during hospital stay

B) Predictive value of PCT, CRP and TLC

PCT and CRP has almost similar predictive value for SIRS and sepsis but PCT has best predictive value for severe sepsis, septic shock, MODS and mortality over CRP and TLC.

Table 7: Relation of PCT with increasing severity of sepsis

		Total (%)	PCT ng/mL	P value
SIRS	Yes	76 (95%)	39.3 (±64.1)	**0.0078**
	No	4 (5%)	0.6 (±1.0)	
Sepsis	Yes	70 (87.5%)	42.5 (±65.9)	**0.0001**
	No	10 (12.5%)	1.4 (±2.8)	
Severe sepsis	Yes	32 (40%)	83.1 (±80.1)	**<0.0001**
	No	48 (60%)	6.9 (±9.3)	
Septic shock	Yes	17 (21.3%)	127.4 (±77.9)	**<0.0001**
	No	63 (78.7%)	13.1 (±26.1)	

Discussion

Prognostication of critically ill children is an important issue in pediatric critical care medicine. Markers that are able to stratify critically ill children depending on the risk of mortality and other outcomes are required to help physicians in making decisions. Bacterial infections are a common cause of PICU admissions in developing countries. PCT is one such marker of systemic inflammation secondary to bacterial infections[11,12,13]. This prospective study was planned to evaluate the utility of admission PCT levels in predicting outcome of critically ill children. Data from this study suggests that PCT levels are raised in patients with suspected bacterial infections and higher concentrations are seen with increasing severity of sepsis (SIRS, sepsis, severe sepsis and septic shock).

Baseline PCT values in study subjects

Data from our study suggests that PCT levels are elevated in most critically ill children admitted to PICU with suspected bacterial infection. In our study, 81.2% had elevated PCT levels. Mean value of baseline PCT was 37.4 ng/mL. Fifteen patients had PCT value of ≤ 0.5ng/mL (Table 2). PCT is a well established marker for systemic bacterial infection. However, localized bacterial infection and non-infective cases may have negative PCT[14,15,16,11,17].

Han et al. [14] in their cohort study on 78 children showed an increase in procalcitonin concentration on day 1 (7.1 ng/ml [0.9–44.8], p<0.001) and on day 3 (2.9 ng/ml [0.1–32.4], p < .05). Procalcitonin concentrations were not increased among children with fungal, viral or culture-negative sepsis vs. controls.

Similarly, Assicot et al[16]. in their study showed that PCT concentration increases with onset of infection and can be correlated with severity of infection (patients with septic shock had PCT up to 200 ng/mL).

Jaresova et al[15]. found that high PCT levels were associated with systemic bacterial infections, and showed minimal or no induction in response to viral infection or rejection episodes. Localized bacterial infections, such as pneumonia, also resulted in only a moderate increase in serum PCT levels.

Simon et al[18]. compared the accuracy of PCT and CRP as diagnostic markers of bacterial infection in critically ill children at the onset of SIRS and concluded that PCT is better than CRP for differentiating bacterial from nonbacterial SIRS in critically ill children, although the accuracy of both tests is moderate.

To summarize, our data is consistent with most previous studies showing elevated PCT levels in critically ill children with suspected bacterial infection.

PCT and Severity scores

We analyzed the relationship between PCT and severity scores (PRISM III score, PIM 2 and Multi organ dysfunction score); and duration of PICU stay. Comparisons were subsequently done with CRP levels. We categorized the patients between 3 groups of severity based on PRISM III score and found that PCT levels were related to severity scores. (Table 4).

Similar association between PCT and severity of disease has been previously reported in many other studies[16,19,20,21].

Our results are consistent with study performed by Qi et al[22]. investigating the correlation between serum PCT level and pediatric critical illness score (PCIS) and their prognostic values in children with sepsis. A combination of serum PCT and PCIS can be used as an early prognostic indicator in children with sepsis.

Flores et al[23]. showed that increase of PCT was higher in patients with shock or multiple organ dysfunction syndrome, having a high severity score (Pediatric Risk of Mortality) or in patients who later died; and PCT have a better prognostic value than CRP or neutrophil count.

PCT and multiorgan dysfunction

In our study, we measured PCT and CRP and compared it with multiorgan dysfunction score. Organ dysfunction was described as per International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics[24]. It was found that those who had multiorgan dysfunction had significantly higher values of PCT (p-value<0.0001) compared to those without multiorgan dysfunction. Such relationship was not observed between CRP and multiorgan dysfunction (p-value 0.1163). A diagnostic cut off value of PCT, 15.5 ng/mL had 70.9% sensitivity and 81.63% specificity to predict multiorgan dysfunction. Sensitivity and specificity of CRP and TLC were 64.5%, 61.2% and 58.1%, 55.1% respectively. This suggests that PCT is a much better predictor of multiple organ dysfunction compared to CRP and TLC.

Our result was in concordance with the studies done by Meisner et al[25], Han et al[14], Hatherhill et al[26]. and Castelli et al[27].

To summarize, baseline PCT levels are related to organ dysfunction. Higher PCT levels are associated with severity of multi organ dysfunction. Meanwhile, CRP levels did not have relation with organ dysfunction.

Association of PCT with complications during hospital stay

In our study, PCT levels were found to be significantly higher in all those who had any of the complications than those who did not. CRP levels were found to be significant only in those who had AKI, coagulopathy and required transfusion of blood products (Table 6, Figure 1).

Hatherhill et al[26]. in their study concluded that admission PCT, TNF and IL-10, is related to the severity of organ failure and mortality in children with septic shock. A fall in PCT after 24 hrs of treatment may have favorable prognostic significance.

To summarize, baseline PCT levels can be related to severity of complications. Higher PCT levels are associated with increased need of supportive care including need of ventilator support, vasopressor support, presence of coagulopathy, AKI and transfusion of blood products.

PCT versus CRP as predictor of mortality

Eighteen children (22.5%) out of 80 enrolled patients died. A diagnostic cut of value of PCT of 18.6ng/mL had 72.2% sensitivity and 75.8% specificity to predict mortality. Sensitivity and specificity

of CRP and TLC were 66.7%, 56.5% and 66.7%, 62.9% respectively. This suggests that PCT is a much better predictor of mortality compared to CRP and TLC.

Jensen et al[28]. from their study concluded that high maximum PCT level and a PCT increase for 1 day are early independent predictors of all-cause mortality in a 90-day follow-up period after ICU admission. Mortality risk increases every day as PCT increases. Levels or increase of CRP and white blood cell count do not seem to predict mortality.

Qi et al[22]. in their study observed that in comparision with the death group, the survival group had significantly higher serum levels of PCT and LA ($P<0.05$) but a significantly lower PCIS ($P<0.05$). For children with sepsis, the lower the PCIS, the higher the serum PCT level, results in a poorer prognosis.

Limitations

1. Sample size of the study was small so it is not possible to generalize the results.
2. We observed much higher PCT levels in children with early mortality. However correlation could not be established because of overall low mortality.
3. Our study conclusions regarding PCT are also limited to a relatively early period of sepsis (within 24 hours), and additional studies examining sequential PCT concentrations at later time points are needed to determine the utility of serial PCT levels.

Conclusion

We observed that PCT levels are high in critically ill children with suspected bacterial infection admitted to PICU. Higher PCT levels are observed in patients with higher severity scores (PRISM III, PIM 2 and MODS). PCT levels were high in patients with multi organ dysfunction. PCT levels were also high in patients having complications (requiring mechanical ventilation, vasopressor support, transfusion of blood products, having acute kidney injury, coagulopathy). Higher PCT levels were found in patients who died. PCT and CRP have similar diagnostic value for predicting SIRS and sepsis. However, PCT is a better diagnostic marker for predicting severe sepsis, septic shock, multi organ dysfunction and mortality.

PCT may become a helpful clinical tool in stratifying pediatric patients with SIRS according to disease severity. PCT estimation is a rapid diagnostic tool which can be used as a prognostic marker for predicting morbidity and mortality in critically children, and should be included in clinical practice in PICU.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

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Conflict of Interest: Nil Source of support: Nil