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# Procalcitonin, C-Reactive Protein and its Correlation with Severity Based on Pediatric Logistic Organ Dysfunction-2 (PELOD-2) Score in Pediatric Sepsis

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**Abstract** **Background:** Periodic procalcitonin (PCT) and C-Reactive Protein (CRP) tests could monitor sepsis response to the therapy, severity, and outcome. Pediatric Logistic Organ Dysfunction Score (PELOD)-2 is a scoring system for predicting organ dysfunction severity progressivity and outcome in critical ill children. The primary endpoint was the correlation of PCT and CRP levels with disease severity based on PELOD-2 score in sepsis children. **Methodology and principal findings:** A correlational analytical cross-sectional non-clinical trials on periodic measurements of 31 sepsis children was conducted from February to April 2016 in Hasan Sadikin General Hospital Bandung, Indonesia. Eligible subjects were newly diagnosed sepsis (aged ≥1 month to 14 years old). PCT and CRP as well as PELOD-2 scores were assessed in all subjects at T1, T2, and T3. During the study period, 31 sepsis children met the inclusion criteria. In the septic shock group, a significant correlation was found between PCT and PELOD-2 at T3 ($p<0,05$), between CRP and PELOD-2 score at T3 ($p<0,05$), and also between PCT and CRP at T2 and T3 ($p<0,05$). In survivor and non survivor, there was a significant difference in PCT level at T2 and T3 as well as in PELOD-2 score at T1, T2, and T3 but with no significant difference in CRP level for the 3 measurement days. **Conclusions:** PCT and CRP levels correlate with disease severity based on PELOD-2 score in children with sepsis.

***Keywords:*** *procalcitonin, C-Reactive Protein, PELOD-2 score, pediatric sepsis*

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## 1. Introduction

Sepsis is a significant cause of morbidity and mortality of infants and children worldwide, particularly in limited resource countries [1]. World Health Organization data have shown that 80% deaths in children less than 4 years are due to sepsis [2]. The Third International Concencus Definitions for Sepsis and Septic Shock (Sepsis-3) define sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [3].

Effective use of blood culture is the gold standard of septic management in infants and children but it requires long time intervals for obtaining results [4]. The traditional clinical signs of infection and routine laboratory tests which used to diagnose sepsis decrease diagnostic accuracy and can be misleading. Physicians need an early and rapid marker for detecting bacterial infection and distinguish it from viral infection [5].

Procalcitonin (PCT) and C-reactive Protein (CRP) are the most frequently used by biomarkers in sepsis. Changes in PCT and CRP concentrations were associated with outcomes of critical ill septic patients [6]. PCT and CRP levels are related to the severity of organ dysfunction, but the concentrations are still higher than during infection. Different sensitivities and kinetics indicate a different clinical use for both parameters [7].

Organ dysfunction score is important to describe and quantify the severity of organ dysfunctions [8]. The Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score is used to assess organ dysfunction in critical ill children. The progression of the severity of organ dysfunctions can be evaluated by measuring the daily PELOD-2 score [9]. There have been no studies on whether these biomarkers (PCT and CRP) and PELOD-2 score are strongly correlated. The aim of our study is to assess the correlations between PCT and CRP with the severity based on PELOD-2 scores in children with sepsis.

## 2. Methods

### 2.1. Patients Population

A correlational analytical cross-sectional non-clinical trial on periodic measurements of 31 sepsis children was conducted from February to April 2016 in Hasan Sadikin General Hospital Bandung, Indonesia. Eligible subjects

were newly diagnosed sepsis (aged ≥1 month to 14 years old). Thyroid carcinoma, hepatic carcinoma, autoimmune disease, surgical and traumatic patients were excluded based on the history taken, physical examination, and/or laboratory test. Subjects were selected through consecutive sampling. The enrollmet and examination of patients was performed by authors and four trained senior residents. Informed consent were obtained from the patients' parents and or guardian simultaneously while performing sepsis management. The Ethics Comittee of Hasan Sadikin Hospital had approved the protocol before the study. PCT and CRP as well as PELOD-2 scores were assessed in all subjects at day 1, day 2, and day 3.

## 2.2. Study Protocol

Patients who met the inclusion criteria, their blood samples were obtained via vascular puncture for PCT and CRP analysis and stored in serum tubes without anticoagulant. The samples were centrifuged and the serum were collected and frozen at -70°C for further processing. Blood cultures were attained using separate vials. Day 1 (T1) was defined as the first observational day at admission, and the next day was named T2 (day 2), then T3 (day 3). PELOD-2 score was also recorded in these 3 consecutive days. The assay for PCT was using Cobas e411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Plasma CRP was measured using a Cobas Integra 400 plus (Roche Diagnostics Ltd, Rotkreuz, Switzerland).

## 2.3. Studied Parameters

All patients had the determination of levels of PCT and CRP, as well as PELOD-2 score to determine the severity of the disease. The examination was done at T1, T2, and T3. Blood culture was collected at T1.

## 2.4. Study Endpoints

The primary endpoint was the correlations between PCT and CRP with the severity based on PELOD-2 scores in children with sepsis.

## 2.5. Sample-size Determination and Statistical Analysis

To calculate the sample size for correlating PCT and CRP with PELOD-2 score, then the sample size is, then determined in relation to the formula to examine the correlation with significance level 95% ($Z\alpha = 1,96$) and power test 80% ($Z\beta = 0,84$). Coefficient correspondence for the correlation between PCT and CRP with PELOD-2 score were assessed using rank Spearman test. Comparisons between groups (survivor and non survivors) were performed by Mann-Whitney test.

P values <0,05 was considered significant. Statistical calculations were performed with SPSS statistical software (version 23.0; SPSS Inc., Chicago, IL, USA).

# 3. Results

## 3.1. Studied Population

Since February to April 2016, 31 patients were assessed for eligibility, no patients were excluded. The 31 patients had been examined for the levels of PCT and CRP, as well as PELOD-2 score at T1, T2, and T3. Figure 1 depicts participants' flow diagram.

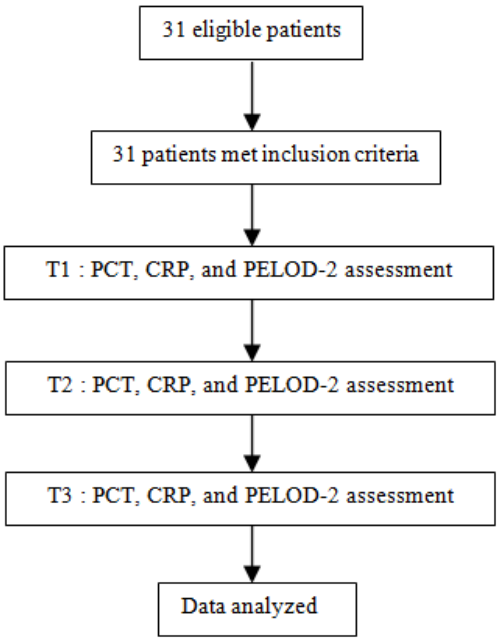


**Figure 1.** Participant's Flow Diagram

The demographic and clinical characteristics of the patients are represented in Table 1. The total genders of 31 patients; were 20 male and 11 female. Most of the patients aged under 5 years. Twelve patients were with sepsis (38,7%) and 19 patients were with septic shock (61,3%). Fourteen patients (45,1%) were treated in pediatric intensive care unit. From the 31 patients, 19 showed positive blood cultures.

**Table 1. Characteristic of Study Patients**

| Variables | Patients |
|---|---|
| **Sex** | |
| Male | 20 |
| Female | 11 |
| **Age** | |
| <1 year | 16 |
| 1–<5 years | 5 |
| 5–<10 years | 6 |
| ≥10–14 years | 4 |
| **Hemodynamic parameter on admission** | |
| Glasgow Coma Scale | 12 (8–14) |
| Mean Arterial Pressure | 45,4 (22–68) |
| **Sepsis type** | |
| Sepsis | 12 |
| Septic shock | 19 |
| **PELOD-2 score on admission** | 5,9 (1–13) |
| **Hospital treatment** | |
| Pediatric Intensive Care Unit | 14 |
| Pediatric ward | 17 |
| **Blood culture result** | |
| Positive blood culture | 19 |
| Negative blood culture | 12 |

## 3.2. PCT, CRP, and PELOD-2 Assessment

The time courses of PCT, CRP, and PELOD-2 score in septic shock patients were analysed and represented in

Table 2. There was a significant correlation between PCT and PELOD-2 score at T3. CRP and PELOD-2 score also showed significant correlation at T3. PCT and CRP showed significant correlation at T2 and T3. Whereas in sepsis patients there were no correlation between PCT with PELOD-2 score, CRP with PELOD-2 score, and PCT with CRP in 3 the measurement days.

**Table 2. Correlation between PCT and CRP with PELOD-2 Score in Sepsis and Septic Shock**

| Variables | p Value* | |
|---|---|---|
| | Sepsis | Septic shock |
| **PCT with PELOD-2 score** | | |
| T1 | 0,886 | 0,701 |
| T2 | 0,630 | 0,164 |
| T3 | 0,442 | <0,001 |
| **CRP with PELOD-2 score** | | |
| T1 | 0,053 | 0,896 |
| T2 | 0,931 | 0,663 |
| T3 | 0,190 | 0,018 |
| **PCT with CRP** | | |
| T1 | 0,430 | 0,204 |
| T2 | 0,656 | 0,016 |
| T3 | 0,759 | 0,001 |

Note: *) Rank Spearman correlation test.

Comparison for PCT, CRP, and PELOD-2 score based on patient outcome as survivor and non-survivor were analysed and represented in Table 3. Of 31 patients, there were 22 survivors and 9 non-survivors. Significant difference was showed on PCT at T2 and T3 between survivor and no-survivor. Significant difference was also presented on PELOD-2 score at T1, T2, and T3. In deceased patients which presented higher PCT value and PELOD-2 score than the patients who survive. However, no significant differences were observed between the two populations in relation to CRP at T1, T2, and T3.

**Table 3. PCT, CRP, and PELOD-2 Score Values In The Study Population and Comparison Between Survivors and Non-Survivors**

| Variables | Pasien Outcome | | p Value |
|---|---|---|---|
| | Survivor | Non-survivor | |
| **PCT** | | | |
| T1 | 1,51 (0,039–15,13) | 2,48 (0,378–25,22) | 0,219* |
| T2 | 1,20 (0,09–27,95) | 15,05 (0,22–61,39) | 0,006* |
| T3 | 1,06 (0,04–87,45) | 27,37 (2,5–48,82) | 0,001* |
| **CRP** | | | |
| T1 | 32,40 (0,20–245,70) | 21,34 (0,38–90,20) | 0,356* |
| T2 | 21,52 (2,00–206,52) | 42,24 (0,70–288,94) | 0,593* |
| T3 | 23,97 (0,80–310,25) | 53,46 (0,80–198,18) | 0,301* |
| **PELOD-2 score** | | | |
| T1 | 5,00 (1–10) | 9,00 (5–13) | <0,001* |
| T2 | 5,00 (0–17) | 9,00 (7–16) | 0,003* |
| T3 | 3,00 (0–11) | 18,00 (12–21) | <0,001* |

Note: *) Mann-Whitney test.

## 4. Discussions

Sepsis remains a major cause of morbidity and mortality among children. The incidence was the highest in infants, the fell dramatically in older children, and was higher in boys than girls. Severe sepsis is a significant health probem in children and is associated with the use of extensive healthcare resources [10,11]. In the present study we found most of our patients' were male whose aged below 5 years.

Sepsis is the primary cause of death from infection, especially if it is not recognized and treated promptly, its recogntion mandates urgent attention [3]. In our study, we found 19 patients with septic shock. We monitored initial mean arterial pressure and PELOD-2 score with median value 12 and mean value 5,9 respectively.

Developing countries with large population of children bear the major burden of pediatirc sepsis. Intensive care supports intervensions to prevent sepsis related to the death and disability which is needed to remedy this issue [12]. Our study found only 14 patients (45,1%) were treated in pediatric intensive care unit.

Both PCT and CRP are accepted sepsis markers. Different sensitivities and kinetics indicate a different clinical use for both parameters [7]. PCT levels were highly correlated with the severity scores regularly used in intensive care units, therefore, can be used for determining the severity of the septic process [13]. The present study showed in septic shock group, there was a significant correlation between PCT and PELOD-2 score at T3.

The use of CRP measurement may have a determining effect on health and progress of clinical cases, as it helps to avoid interpretation errors and improper interventions, such as in sepsis [14]. This study showed significant correlation between CRP with PELOD-2 score at T3.

The use of assays in sepsis biomarkers, PCT and CRP, were found to be suitabe for sepsis diagnosis [15]. Changes in PCT and CRP levels may be favoured in judging response to antibiotic treatment, while the latter may best indicate the complications risk, such as bloodstream infection, septic shock, organ failure and mortality [16]. This is the first study which correlating PCT and CRP to PELOD-2 score. In this study, PCT values were correlated to CRP at T2 and T3. It was observed that the level of serum PCT and CRP serum increase the severity of sepsis and organ dysfunction which could also be used to identify patients with high risk of adverse outcomes.

Biomarkers have proven a suitable method for predicting clinical outcomes in septic patients. Both PCT and CRP levels are commonly measured in septic patients [17]. PCT and CRP levels are related to the severity of organ dysfunction, but concentrations were still higher than during infections [7]. This study showed the values of PCT which correlated with those of CRP that could help us determines whether the infectious process is of bacterial origin or not, if the patient has a septic process and determines the severity of illness. The determination of PCT and CRP could be a best tool to define sepsis activity and prognosis than the parameters currently used.

Persistently high PCT concentrations in plasma, as well as reduced 24-hours PCT clearance, were associated with a significant increase in mortality to the patients with severe sepsis and septic shock [18]. PELOD scoring system can be used to determine the patients' probability of death in pediatric intensive care unit [19]. Our study showed significant difference on PCT at T2 and T3 between survivor and non-survivor. Significant difference

was also showed on PELOD-2 score at T1, T2, and T3. However, no significant differences were observed between the two populations in relation to CRP at T1, T2, and T3. It was also discovered that the level of PCT and CRP fell over the course of in-hospital stay in survivors which might be due to the fact that they were acute inlammatory reactans and the levels were improving by the time.

There are certain limitations to this study that merit consideration. First, this study was a single-center study so further multicenter study is required to investigate whether our results are applicable to all children with sepsis. Secondly, our study conducted assessment in only 3 monitoring days. It is advisable to monitor PCT, CRP and PELOD-2 score from admission day to patient discharge or death. The reliability of a marker for sepsis/septic shock depends on the precision of clinical diagnosis, which should be sought ceaselessly in order to perfect clinical definitions, especially in children.

## 5. Conclusions

We concluded that PCT and CRP elevation were correlated with severity of the illness and as an early marker of sepsis. The use of serial PCT and CRP determinations increase the diagnostic reliability and can even guide us regarding the suitability of the treatment provided.

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