

# The Clinical Usefulness of Procalcitonin Measurement for Assessing the Severity of Bacterial Infection in Critically Ill Patients Requiring Corticosteroid Therapy

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## Abstract

Markers of inflammation, such as C-reactive protein (CRP) and white blood cell count, have, because of their low specificity, proven far from ideal in identifying patients with sepsis. Procalcitonin (PCT) has been shown to be a useful marker for differentiating patients with bacterial infection from other acute inflammatory conditions. Corticosteroid therapy has been demonstrated to be effective for treating patients with septic shock, late-phase acute respiratory distress syndrome (ARDS), or functional adrenal insufficiency, and the use of corticosteroid in critical illness has recently increased. It is also well established that corticosteroid modulate inflammatory variables in acute inflammatory conditions. The purpose of this study was to evaluate the clinical usefulness of PCT measurement for assessing the severity of bacterial infection in patients requiring corticosteroid therapy.

**Materials and Methods:** Six patients with confirmed bacterial infectious diseases or suspected infectious diseases and requiring corticosteroid therapy were enrolled in the study. Levels of PCT and CRP were measured. The Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were calculated to evaluate the severity of sepsis.

**Results:** 1) There was no significant correlation between the serum concentration of PCT and the plasma level of CRP in patients requiring corticosteroid therapy. 2) The PCT concentration was significantly correlated with the SOFA score ( $R^2=0.467$ ,  $p<0.0001$ ) and the APACHE II score ( $R^2=0.308$ ,  $p=0.0003$ ). However, no significant correlations was found between the CRP concentration and the SOFA score ( $R^2=0.054$ ,  $p=0.15$ ) or the APACHE II score ( $R^2=0.043$ ,  $p=0.20$ ). 3) Data sets were divided into two groups: septic shock and non-septic shock. No significant differences were present in CRP levels between the groups. However, significant differences were apparent in PCT concentrations ( $p<0.001$ ).

**Conclusion:** PCT can be a more sensitive and useful marker than CRP for evaluating the severity and progression of sepsis in patients requiring corticosteroid therapy. Further studies are needed to confirm these results in larger groups of patients.

(J Nippon Med Sch 2007; 74: 236–240)

**Key words:** procalcitonin, sepsis, corticosteroid, critical ill

## Introduction

Sepsis is a major cause of mortality in the intensive care unit. Because early detection and specific clinical intervention are crucial for favorable outcomes in patients with sepsis, great efforts have been made to reduce the time needed to diagnose sepsis to reduce mortality from sepsis-related multiple organ failure<sup>1,2</sup>. However, sepsis can be difficult to distinguish from other noninfectious conditions with clinical signs of acute inflammation. Although bacterial culture is the best method for diagnosing infection, it does not indicate the host response well or differentiate between bacterial colonization and systemic complication and requires more than 24 hours. Markers of inflammation, such as C-reactive protein (CRP) and white blood cell count (WBC), have proven far from ideal in identifying critically ill patients who need antimicrobial therapy, because the sensitivity and specificity for bacterial infection are quite low<sup>3,4</sup>.

Procalcitonin (PCT) was initially described as a prohormone of calcitonin, a hormone of the calcium metabolism produced in the medullary C-cells of the thyroid gland<sup>5-7</sup>. Recent studies have demonstrated that variant PCT associated with infection can be produced by many other tissues<sup>8-10</sup>. PCT has also been shown to be a useful marker for differentiating bacterial infection from other acute inflammatory conditions and for assessing the severity of bacterial infection<sup>11-13</sup>.

Corticosteroid therapy has been demonstrated to be effective for treating patients with septic shock, late-phase acute respiratory distress syndrome (ARDS), or functional adrenal insufficiency, and the use of corticosteroid in critical illness has recently increased<sup>14-17</sup>. While it is well established that corticosteroids modulate inflammatory variables, such as body temperature, the CRP level, and the WBC count, in acute inflammatory conditions<sup>18-20</sup>, the effect of corticosteroid therapy on serum levels of PCT in patients with sepsis is unclear.

The purpose of this study was to evaluate the clinical usefulness of PCT measurement for assessing the severity of bacterial infection in patients requiring corticosteroid therapy.

## Materials and Methods

Six patients with confirmed bacterial infectious diseases or suspected infectious diseases and requiring corticosteroid therapy were enrolled in the study (1 man and 5 women; mean age,  $67.8 \pm 9.0$  years). The infectious foci were the lower respiratory tract in 4 patients and peritoneum in 2 patients.

Measurement of serum PCT level has been approved by the Japanese Ministry of Health, Labour and Welfare to evaluate sepsis and bacterial infection. Blood samples were obtained as part of the routine clinical and laboratory work-up, and data were collected retrospectively.

The indications for corticosteroid therapy were bronchial asthma (1 patient; prednisolone, 40 mg/day), rheumatoid arthritis (1 patient; prednisolone, 10 mg/day), interstitial pneumonitis (1 patient; methylprednisolone sodium succinate, 500 mg/day for 3 days and tapered thereafter), late-phase ARDS (2 patients; methylprednisolone sodium succinate, 2 mg/kg/day and tapered thereafter according to a protocol published previously<sup>21</sup>), and septic shock (1 patient; hydrocortisone sodium succinate, 200 mg/day for 14 days).

Levels of PCT and CRP were measured as inflammatory markers, and the Sequential Organ Failure Assessment (SOFA) score, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were calculated to evaluate the severity of sepsis in the 6 patients when the bacterial infectious disease was diagnosed or when infectious diseases was suspected, and daily thereafter for 7 days (total 40 time points). Serum PCT concentrations were measured with an immunoluminometric assay (LUMI test PCT; Brahms Diagnostica, Berlin, Germany).

### Statistical Analysis

Data are expressed as means  $\pm$  standard deviations. Correlations were analyzed with Spearman's rank-correlation test. The significance of differences between groups was determined with the Mann-Whitney U test. Statistical significance was accepted when  $p < 0.05$ .

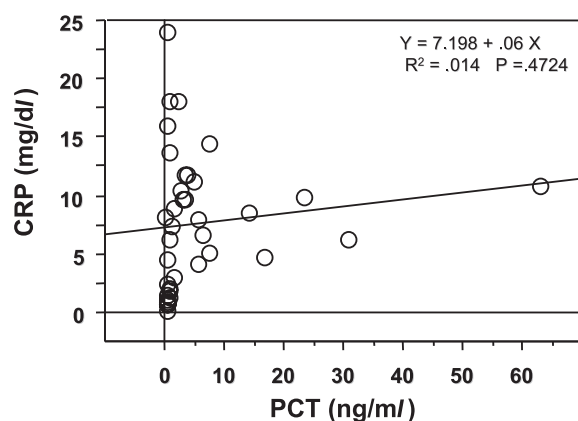


Fig. 1 Relationship between PCT and CRP in patients with confirmed bacterial infection or suspected infectious disease requiring corticosteroid therapy

## Results

### Relationship between PCT and CRP (Fig. 1)

There was no significant correlation between the serum concentration of PCT and the plasma level of CRP in patients who had bacterial infectious diseases or were suspected of having infectious diseases and required corticosteroid therapy.

### Relationships between PCT, CRP, SOFA Score, and APACHE II Score

The PCT concentration was significantly correlated with the SOFA score ( $R^2=0.467$ ,  $p<0.0001$ ) and the APACHE II score ( $R^2=0.308$ ,  $p=0.0003$ ) (Fig. 2). However, no significant correlations were found between the CRP concentration and the SOFA score ( $R^2=0.054$ ,  $p=0.15$ ) or the APACHE II score ( $R^2=0.043$ ,  $p=0.20$ ) (Fig. 3).

### Comparison of PCT and CRP between Septic Shock and Non-septic Shock

Data sets were divided into two groups depends on patients' status according to the definition of the 1991 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis<sup>22</sup>: septic shock ( $n=10$ ) and non-septic shock ( $n=30$ ). No significant differences were present in CRP levels between the groups. However, significant differences were apparent in PCT concentrations

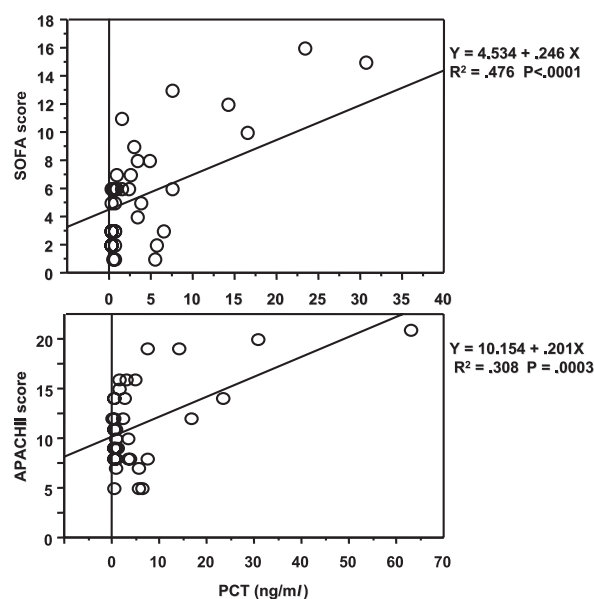


Fig. 2 Relationships between PCT, SOFA score, and APACHE II score

The PCT concentration was significantly correlated with the SOFA score ( $R^2=0.467$ ,  $p<0.0001$ ) and the APACHE II score ( $R^2=0.308$ ,  $p=0.0003$ ).

between the groups (Fig. 4).

## Discussion

In this study, PCT has been shown to be a more sensitive and useful marker than CRP for evaluating disease severity as measured with the SOFA score and the APACHE II score in patients with sepsis who require corticosteroid therapy.

The roles of PCT, its sites of production, and the mechanism underlying PCT induction are still unclear<sup>23,24</sup>. Recent findings suggest that sources of PCT in systemic inflammatory conditions are extrathyroidal and may include hepatic cells and monocytes/macrophages<sup>8-10,25,26</sup>. Increasing serum PCT levels have been demonstrated to be a more reliable diagnostic and prognostic marker than other inflammatory markers, such as CRP, interleukin-6, interleukin-8, lactate, and the WBC count in patients with severe bacterial infection<sup>13,27-30</sup>.

Although the role of corticosteroid therapy during sepsis is still controversial, low-dose corticosteroids have beneficial effects in patients with septic shock-associated functional adrenal insufficiency and late-phase ARDS<sup>14-17</sup>. It is well established that corticosteroid therapy changes inflammatory

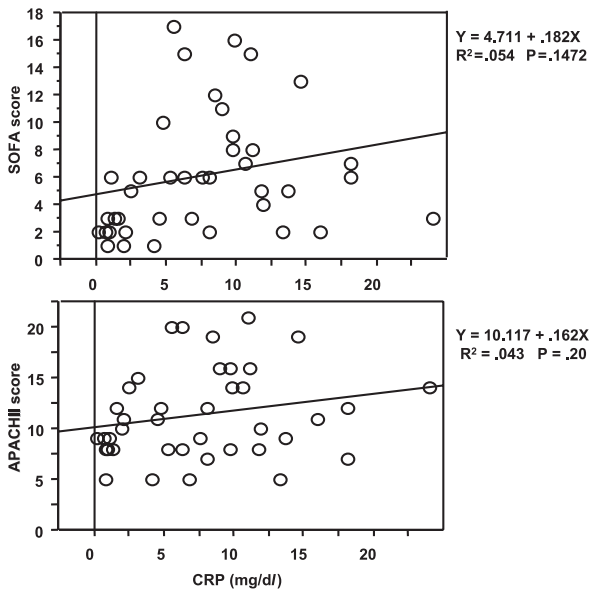


Fig. 3 Relationships between CRP, SOFA score, and APACHE II score  
No significant correlation was found between the CRP concentration and the SOFA score ( $R^2=0.054$ ,  $p=0.15$ ) or the APACHE II score ( $R^2=0.043$ ,  $p=0.20$ ).

variables, such as CRP level and the WBC count, in acute inflammatory conditions and dose-dependently modulate the stress response by preventing an excessive inflammatory response<sup>18-20</sup>. To date, however, little is known about the clinical value of PCT in patients with bacterial sepsis requiring corticosteroid therapy.

A limitation of this retrospective study is that it includes only a small number of patients and wide variations in the type and dose of corticosteroids. In particular, the type and dose of corticosteroids used differ with the patients conditions, such as rheumatoid arthritis, bronchial asthma, and septic shock, and can have significant effects on the clinical course and changes in inflammatory markers. It is well known that corticosteroids modulate inflammatory response dose-dependently and that the strength of the effect varies with the corticosteroid type<sup>31</sup>. To clarify the effects of corticosteroids on serum levels of PCT, studies must compensate for the effects of predisposing conditions and the type and dose of corticosteroids.

Although it is difficult to evaluate the diagnostic reliability of PCT for bacterial sepsis in patients requiring corticosteroid therapy, the present study has been shown PCT to be a more sensitive and

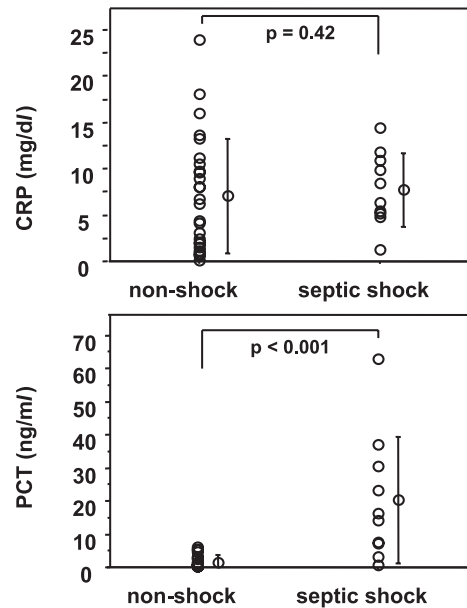


Fig. 4 Comparison of PCT and CRP between septic shock, and non-septic shock  
Data sets were divided into two groups: septic shock ( $n=10$ ) and non-septic shock ( $n=30$ ). No significant differences were present in CRP levels between the groups. However, significant differences were apparent in PCT concentrations.

useful marker than CRP for evaluating the severity and progression of sepsis in patients who require corticosteroid therapy. Further studies are needed to confirm these results in larger groups of patients.

**Acknowledgements:** This manuscript has been published in part as an abstract form of this journal<sup>32</sup>, and also in a Japanese-language journal<sup>33</sup> and permission to submit this manuscript to an English-language journal has been obtained from the publisher.

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(Received, November 27, 2006)

(Accepted, February 13, 2007)