



## Original Article

## Semi-quantitative Procalcitonin Test for the Diagnosis of Bacterial Infection: Clinical Use and Experience in Japan

Hideto Oshita\*, Joji Sakurai, Masakazu Kamitsuna

Department of Respiratory Medicine, Chugoku Rosai General Hospital, Hiroshima, Japan.

**BACKGROUND/PURPOSE:** The efficacy of the rapid semi-quantitative procalcitonin (PCT) test for the diagnosis of bacterial infection was evaluated in patients with systemic inflammatory response syndrome.

**METHODS:** A retrospective observational study was performed from June to December 2008 at the Chugoku Rosai General Hospital, Japan. This study analyzed consecutive patients (both outpatients and inpatients) who developed systemic inflammatory response syndrome and whose PCT test was measured semi-quantitatively within 24 hours of onset, or at the first hospital visit. Based on the clinical diagnosis, the patients were divided into two groups. Group I comprised patients with a bacterial infection, and group II comprised patients with a non-bacterial infection, or non-infectious disease. Receiver operating characteristic curves were used to evaluate the diagnostic value of the semi-quantitative PCT test kit, C-reactive protein levels and white blood cells counts for the detection of bacterial infections, and the areas under the resulting curves were compared.

**RESULTS:** A total of 168 patients were included and divided into groups I ( $n=112$ ) and II ( $n=56$ ). Group I showed a significantly higher percentage of positive PCT tests ( $\geq 0.5$  ng/mL) than group II (67.8% vs. 19.6%,  $p<0.001$ ). PCT showed a sensitivity of 67.8% [95% confidence interval (CI)=58.4–76.4] and a specificity of 80.4% (95% CI=67.6–89.8). The areas under the resulting curves for PCT (0.764) were significantly larger than those seen for C-reactive protein (0.650,  $p=0.02$ ) and white blood cells (0.618,  $p=0.006$ ).

**CONCLUSION:** The semi-quantitative PCT test is as useful for distinguishing bacterial infection from other inflammatory diseases in common clinical practice as the quantitative PCT.

**KEYWORDS:** C-reactive protein, diagnostic accuracy, inflammation marker, procalcitonin, white blood cell counts

\*Corresponding author. Department of Respiratory Medicine, Chugoku Rosai General Hospital 1-5-1, Hiro-Tagaya, Kure-shi, Hiroshima 737-0193, Japan.

E-mail: [internal.medicine.crgh@gmail.com](mailto:internal.medicine.crgh@gmail.com)

### Article History:

Received: Feb 5, 2009

Revised: May 2, 2009

Accepted: Jul 15, 2009

### Introduction

Procalcitonin (PCT) is the precursor of calcitonin, and is normally produced in the C-cells of the thyroid gland.<sup>1</sup> During systemic and severe infections, PCT is also produced rapidly in other tissues, and serum PCT concentrations increase to very high levels.<sup>2,3</sup> Assicot et al first described PCT as an inflammation-induced protein in 1993.<sup>4</sup> Since then, numerous clinical studies have demonstrated the utility of this marker. PCT is more

specific for detecting bacterial infection than other inflammatory markers, such as C-reactive protein (CRP) and white blood cell counts (WBC), because viral infections, autoimmune and allergic disorders do not induce PCT.<sup>5,6</sup>

Systemic inflammatory response syndrome (SIRS) is a new concept of inflammation that was suggested in 1991 to detect patients likely to develop severe sepsis.<sup>7</sup> Determining whether a bacterial infection is present in a patient with SIRS can be the first step to appropriate treatment. However, clinicians often have difficulty with the diagnosis because SIRS can have various causes. Therefore, developing a diagnostic method that can detect a bacterial infection easily and rapidly would be very helpful.

Measurement of PCT is common worldwide, and quantitative and semi-quantitative methods for measuring this marker have been available in Japan since 2006. There have been several studies that have evaluated the usefulness of quantitative PCT measurements for the diagnosis of bacterial infections in patients with SIRS.<sup>8,9</sup> However, the usefulness of the semi-quantitative PCT test kit has not been suitably evaluated. We compare the semi-quantitative PCT test, which can be performed easily at the bedside and require only small amount of blood samples, with CRP and WBC for the diagnosis of bacterial infections in patients with SIRS.

## Methods

### Patients

A single-center retrospective observational study was performed from June 1 to December 18, 2008 at the Chugoku Rosai General Hospital, Hiroshima, Japan. This urban hospital primarily serves a general population and has about 8,000 admissions each year. This study analyzed consecutive patients (outpatients and inpatients) that developed SIRS, and a semi-quantitative PCT test was performed within 24 hours of onset, or at the first visit to hospital. Patients younger than 15 years of age were excluded. SIRS was defined by two or more of the following objective measurements: body temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ ; heart rate  $>90$  beats/min; respiratory rate  $>20$  breaths/min or  $\text{PaCO}_2 <32$  mmHg; WBC  $>12 \times 10^9/\text{L}$  or  $<4 \times 10^9/\text{L}$  or  $>10\%$  immature forms.

On the basis of the final clinical diagnosis, the patients were divided into two groups: group I comprised those patients with a bacterial infection, and group II comprised those with a non-bacterial infection or a non-infectious disease. When there was no evidence of a non-bacterial infection or a non-infectious disease, a clinical diagnosis of bacterial infection was established if causative bacteria were isolated from various samples (blood cultures, sputum, pus, stool, or urine), if serum or urine samples were positive for bacterial antigens (e.g. *Streptococcus pneumoniae* and *Legionella*), or if the patient was strongly suspected of having a bacterial infection according to clinical data and their clinical course as determined by the attending physician. Any patient who could not be categorized into either of the groups was excluded.

### Measurements

Serum PCT levels were measured in all patients using the PCT-Q test kit (BRAHMS, Germany). This test kit is based on the immunochromatographic principles for semi-quantitative determination of PCT. The test procedure is carried out on non-hemolyzed blood samples that have been centrifuged. Briefly, 200  $\mu\text{L}$  of serum is pipetted into the round cavity of the test strip. The tracer binds to any PCT in the sample and a marked antigen-antibody complex is formed. This complex moves by means of capillary action through the test system, and in the process, passes through an area containing the test band. Here, the marked antigen-antibody complex binds to the fixed anti-calcitonin antibodies and forms a sandwich complex. At a PCT level of  $\geq 0.5$  ng/mL, this sandwich complex can be seen as a reddish band.

The color intensity of the band is directly proportional to the PCT concentration of the sample, and it is related to different PCT level ranges ( $\geq 0.5$  ng/mL,  $\geq 2.0$  ng/mL,  $\geq 10$  ng/mL) with the help of a reference card. Non-bound tracer diffuses into the control band zone, where it is fixed and produces an intense red control band. The functional ability of the test system is then checked by means of this control band. After an incubation period of 30 minutes, the results are observed and the serum PCT concentration ranges are determined by comparing the color intensity of the band with the color blocks on the reference card. Usually, a PCT level  $\geq 0.5$  ng/mL is considered to be positive for the diagnosis of a bacterial infection.

For the measurement of CRP, a latex agglutinating immunoassay reagent, LZ test “EIKEN” CRP (EIKEN Chemicals, Tokyo, Japan), was applied to an automatic biochemical analyzer (TBA-c8000, Toshiba, Tokyo, Japan) in the hospital biochemistry laboratory. WBC were measured in the hospital hematology laboratory.

### Statistical analysis

Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the  $\chi^2$  test (Fisher’s exact test was used when applicable). To compare the clinical value of PCT, CRP, and WBC for detecting bacterial infections, receiver-operating characteristic (ROC) curves were drawn and the areas under

the curves (AUC) were compared. All values of  $p < 0.05$  were considered statistically significant. MedCalc 10.0 for Windows (MedCalc Software, Mariakerke, Belgium) was used for the analysis.

### Results

The characteristics, clinical data and diagnoses of the patients in each group are shown in Tables 1–3. Respiratory infections (57/112; 50.9%) and abdominal infections (39/112; 34.8%) accounted for the majority of the patients in group I (Table 2). Group II included patients with malignant diseases, viral infections, drug-induced inflammation and allergic diseases (Table 3). As shown in Table 1, age, CRP,

**Table 1.** Clinical data of the patients in this study<sup>a</sup>

	Group I (n=112)	Group II (n=56)	<i>p</i>
Sex, male	71 (63.4)	41 (73.2)	0.690
Age (yr)	76 (16–99)	69 (19–94)	0.009
PCT (ng/mL)			
<0.5	36 (32.1)	45 (80.4)	0.001
0.5–1.9	24 (21.4)	7 (12.5)	
2.0–9.9	22 (19.6)	2 (3.6)	
≥10	30 (26.8)	2 (3.6)	
Positive (≥0.5)	76 (67.8)	11 (19.6)	0.001
CRP (mg/dL)	12.2 (0.06–36.50)	8.0 (0.08–25.70)	0.002
WBC (×10 <sup>9</sup> /L)	10.96 (1.34–28.87)	9.04 (4.28–22.81)	0.013
Blood culture collection	67 (59.8)	20 (35.7)	0.005
Positive blood culture	26	1 <sup>b</sup>	0.005
Death within 30 days of onset or first visit	17 (15.2)	4 (7.1)	0.210

<sup>a</sup>Data presented as *n* (%), median (range) or *n*; <sup>b</sup>patient with fungemia. PCT=Procalcitonin; CRP=C-reactive protein; WBC=white blood cells counts.

**Table 2.** Clinical diagnoses of Group I patients (n=112)<sup>a</sup>

Diagnosis	Respiratory infection (n=57)	Abdominal infection (n=39)	Urinary infection (n=9)	Others <sup>b</sup> (n=7)
PCT ≥0.5 (ng/mL)	30 (52.6)	34 (87.2)	7 (77.8)	5 (71.4)
CRP (mg/dL)	12.50 (1.10–36.50)	8.40 (0.06–33.30)	12.90 (0.95–18.90)	24.10 (3.00–27.80)
WBC count (×10 <sup>9</sup> /L)	10.93 (1.91–28.87)	11.44 (1.34–27.37)	9.94 (6.67–17.63)	13.61 (6.45–26.32)

<sup>a</sup>Data presented as *n* (%) or median range; <sup>b</sup>others include cases of soft tissue infection, endocarditis, catheter infection, and meningitis. PCT=Procalcitonin; CRP=C-reactive protein; WBC=white blood cells.

**Table 3.** Clinical diagnoses of Group II patients ( $n=56$ )<sup>a</sup>

Diagnosis	Malignant disease ( $n=12$ )	Viral infection ( $n=12$ )	Allergic disease ( $n=5$ )	Drug-induced inflammation ( $n=5$ )	Others <sup>b</sup> ( $n=22$ )
PCT $\geq 0.5$ (ng/mL)	4 (33.3)	2 (16.7)	1 (20.0)	0	4 (18.2)
CRP (mg/dL)	13.90 (1.70–22.10)	4.90 (0.08–16.70)	6.40 (3.90–22.10)	9.20 (1.20–12.70)	4.20 (0.14–25.70)
WBC count ( $\times 10^9/L$ )	11.59 (6.71–22.81)	8.12 (4.28–14.67)	6.70 (5.38–7.48)	8.58 (5.63–17.65)	9.63 (5.17–20.44)

<sup>a</sup>Data presented as  $n$  (%) or median (range); <sup>b</sup>others include cases of idiopathic interstitial pneumonia, endocrine disease, cardiac disease, trauma, fungal infection and pancreatitis. PCT=Procalcitonin; CRP=C-reactive protein; WBC=white blood cells.

**Table 4.** Diagnostic performance of the semi-quantitative procalcitonin test, C-reactive protein and white blood cells counts for the diagnosis of bacterial infection<sup>a</sup>

Cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PCT (ng/mL)				
$\geq 0.5$	67.8 (58.4–76.4)	80.4 (67.6–89.8)	87.4 (78.5–93.5)	55.6 (44.1–66.6)
$\geq 2.0$	46.4 (37.0–56.1)	92.9 (82.7–98.0)	92.9 (82.7–98.0)	46.4 (37.0–56.1)
$\geq 10.0$	26.8 (18.9–36.0)	96.4 (87.7–99.5)	93.7 (79.2–99.1)	39.7 (31.4–48.4)
CRP (18.5 mg/dL)	37.5 (28.5–47.1)	92.9 (82.7–98.0)	91.3 (79.2–97.5)	42.6 (33.7–51.9)
WBC count ( $9.13 \times 10^9/L$ )	74.1 (65.0–81.9)	51.8 (38.0–65.3)	75.5 (66.3–83.2)	50 (36.6–63.4)

<sup>a</sup>Data presented as % (95% confidence interval). PCT=Procalcitonin; CRP=C-reactive protein; WBC=white blood cells.

WBC and the number of positive blood cultures all showed statistically significant differences between the two groups.

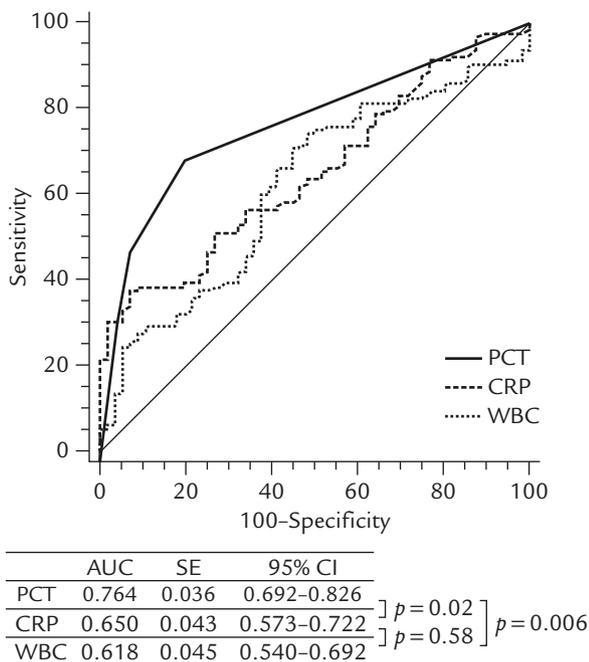
A significantly higher percentage of positive ( $\geq 0.5$  ng/mL) PCT tests were observed in group I than group II (67.8% vs. 19.6%,  $p < 0.001$ ). Overall, the PCT test showed a specificity of 80.4% for detecting bacterial infections. In group II, 11 patients had false-positive results. Although the majority of them had a slightly increased PCT level ( $\geq 0.5$  ng/mL and  $< 2.0$  ng/mL), four of the patients (2 with malignant disease, 1 with thyroid storm, and 1 with non-ketotic hyperglycemic-hyper-osmolar coma) showed high PCT ( $\geq 2.0$  ng/mL) values. Moreover, different sensitivities, specificities, positive predictive values, and negative predictive values were observed when the cutoff values were changed to  $\geq 2.0$  ng/mL and  $\geq 10$  ng/mL (Table 4). On analysis of the infected organs, the percentage of positive PCT tests was significantly lower in those patients with respiratory infection than in those with other organ infections

(52.6% vs. 83.6%,  $p < 0.001$ ), despite relatively high CRP levels and WBC.

Analysis of the ROC curves revealed AUCs of 0.764 for PCT, 0.650 for CRP, and 0.618 for WBC (Figure). Comparison of the AUC for PCT with those of CRP ( $p = 0.02$ ) and WBC ( $p = 0.006$ ) showed a statistically significant difference. At the best cutoff values for PCT (0.5 ng/mL), CRP (18.5 mg/dL), and WBC ( $9.13 \times 10^9/L$ ), the sensitivity and specificity were 67.8% and 80.4%, 37.5% and 92.9%, 74.1% and 51.8%, respectively.

## Discussion

In the current study, PCT showed a significantly higher positive rate of detection in patients with bacterial infection than in other patients. In addition, a comparison of the AUC showed that PCT has a greater diagnostic value than CRP and WBC.



**Figure.** Receiver operating characteristic curves for the semi-quantitative procalcitonin test, C-reactive protein, and white blood cell counts used for the diagnosis of bacterial infection. AUC=Area under the curve; SE=standard error; CI=confidence interval; CRP=C-reactive protein, PCT=procalcitonin; WBC=white blood cells counts.

This study has two limitations. First, the clinicians were not blind to the PCT test results. Therefore, several clinicians might have been influenced by the PCT test results when they determined whether a bacterial infection was present in the patients. The diagnostic value of PCT might have been overestimated. Second, it was unnecessary to identify the causative bacteria in the diagnosis of a bacterial infection. Because we tried to evaluate the value of PCT in common clinical practice, those patients in whom the PCT test was carried out were included whenever possible. As a result, patients with a spurious bacterial infection could have been included in group I and the diagnostic value of PCT might have been underestimated. Nevertheless, it is interesting to note that PCT showed greater a diagnostic value than either CRP or WBC despite such an unfavorable situation.

The sensitivity and specificity of PCT can be changed depending on the study population, cutoff value etc. For example, in a study involving a lot of severely ill patients, PCT shows high sensitivity. The current study included patients with SIRS who are encountered routinely in common clinical practice, a lot of patients with mild bacterial

infections were included. Therefore the sensitivity of PCT was not high. Aikawa et al and Delèveaux et al assessed the diagnostic value of quantitative PCT measurement in populations similar to those in the current study.<sup>8,9</sup> Although the specificity was somewhat inferior, the performance of the semi-quantitative PCT tests in the current investigation (sensitivity=67.8%; specificity=80.4%) was similar to that seen in their reports (cutoff value=0.5 ng/mL; sensitivity=64.4–65.0%; specificity=86.4–96.0%). When a PCT measurement is used in a patient with SIRS, it has low sensitivity and high specificity for detecting bacterial infections. In other words, this marker is ineffective for screening for bacterial infections, but is useful for definitive diagnosis. A patient with a positive PCT test must, therefore, be suspected of having a bacterial infection, and blood cultures and antibacterial therapy are strongly recommended. If PCT shows higher levels ( $\geq 2.0$  ng/mL or  $\geq 10$  ng/mL), this suspicion becomes even stronger. In contrast, one cannot rule out a bacterial infection in a patient with a negative PCT test. In this case, further examinations must be undertaken to determine the presence of a bacterial infection.

The present study showed major difference in the sensitivity of the semi-quantitative PCT test between respiratory infections and other organ infections. We think one of the reasons is that the frequency of involvement of Gram-positive bacteria in respiratory infection is higher than in other organ infection. Gram-positive bacterial infection tends to remain local inflammation, compared to Gram-negative bacterial infection that is susceptible to endotoxin shock. Several investigators have reported that serum PCT levels tend to be higher during episodes of systemic inflammation or Gram-negative bacterial infection than those of local inflammation or Gram-positive bacterial infection.<sup>10,11</sup>

Clinical simplicity and speed are the greatest advantages of the semi-quantitative PCT test. This kit is therefore useful for the diagnosis of patients with SIRS in an emergency room, or under-equipped medical clinics. However, there are several disadvantages compared with quantitative PCT measurements. First, the diagnostic precision of the semi-quantitative PCT test kit is inferior to that of quantitative PCT measurements because the results must be determined visually.<sup>12,13</sup> Laboratory technicians must decide between either the next lower or higher category at

borderline levels. This could introduce a large error if they are not skilled in the use of this kit. The specificity found in this study was lower than that found for quantitative PCT measurements in past reports because the decision as to whether a PCT value of  $\geq 0.5$  ng/mL could be subjective when using the semi-quantitative PCT test. Second, the semi-quantitative PCT test may be a poor tool for sequential evaluation of a patient's condition because the test kit only provides an estimate of serum PCT levels.<sup>13</sup> Serum PCT levels are occasionally increased to  $\geq 100$  ng/mL in patients with severe bacterial infections. Naturally, such a patient would be judged as having a PCT level  $\geq 10$  ng/mL by the semi-quantitative PCT test kit. After treatment, the level will remain at  $\geq 10$  ng/mL according to this test kit if the serum PCT levels do not decrease to  $< 10$  ng/mL, despite an improvement in the patients' condition. In such situations, other quantitative inflammatory markers (e.g. CRP and WBC) may be more useful.

Because the value of measuring PCT in the management of infectious disease is obvious, it is hoped that quantitative PCT measurements can be extensively applied in the near future. However, the results of the current study suggest that the rapid semi-quantitative PCT test kit is sufficient to accurately diagnose bacterial infections in common clinical practice.

## Acknowledgments

We are grateful to the senior residents and laboratory technicians of the Chugoku Rosai General Hospital for collecting the clinical data. We thank Dr Satoko Oshita for technical advice and assistance with translation.

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